ISSN: 3081-1562

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

Archivos de Neurociencias

Volume 29. Number 3, July-September 2024

www.archivosdeneurociencias.mx

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ISSN: 3081-1562
Ref.: 10647AMEX243

Archivos de Neurociencias

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EDITORIAL

Research proposal on the relationship of plasma taurine concentration with cerebral edema in neurosurgical patients

Propuesta de investigación sobre la relación de la concentración plasmática de taurina con el edema cerebral en pacientes neuroquirúrgicos

Iván Pérez-Neri[1]* *and Luisa Manrique-Carmona*[2†]

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[†]*In memoriam*

The management of cerebral edema during the perioperative period for various neurosurgical conditions remains challenging in our routine clinical practice. The difficulty in obtaining an objective diagnosis of the presence of edema has directed medical science efforts toward identifying useful biological markers that can be measured in peripheral blood and indicate the behavior of cerebral edema in different conditions. Two former studies conducted by our research group[1,2] indicate that plasma taurine concentration may fulfill the desired profile.

Intracranial tumors commonly develop chronic cerebral edema, characterized by excessive fluid accumulation in both intra- and extracellular spaces, as well as the formation of new blood vessels that supply the tumor and its surroundings. In contrast, vascular disease (specifically subarachnoid hemorrhage) is an opportunity to study the evolution of cerebral edema and analyze its acute behavior and response to therapy. Intracranial pressure is affected by physiological and pathological changes of cranial content, such as those caused by edema. Therefore, obtaining a real-time objective measurement of this parameter and analyzing its relationship with plasma taurine concentrations could confirm our findings on the increase in taurine concentration and the severity of cerebral edema.

In a previous research protocol, we aimed to compare the effect of intraoperative IV lidocaine infusion vs a control infusion to assess its potential anti-edema effect and its relationship with plasma taurine concentration, as we discussed earlier[3]. The general data of this protocol were:

- Research question: What is the effect of transanesthetic lidocaine infusion on cerebral edema caused by subarachnoid hemorrhage?
- Objective: To determine the effect of continuous lidocaine infusion on cerebral edema caused by subarachnoid hemorrhage.
- Hypothesis: IV lidocaine infusion reduces cerebral edema caused by subarachnoid hemorrhage.
- Problem statement: Perioperative cerebral edema is challenging in the treatment of subarachnoid hemorrhage, as it increases morbidity, complications, and the length of stay.
- Justification: The presence of cerebral edema affects the progression of patients with subarachnoid hemorrhage; timely detection and treatment will positively impact prognosis. Having strategies to treat cerebral edema in subarachnoid hemorrhage will reduce complications and improve outcomes, leading to a shorter length of stay.

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000017

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):65-66
www.archivosdeneurociencias.mx

– Design: The first phase proposed a cross-sectional study to measure plasma taurine concentration in peripheral blood and intracranial pressure during the perioperative period in patients with subarachnoid hemorrhage undergoing aneurysm clipping. Subsequently, a controlled, randomized, double-blind clinical trial would be developed, involving patients with subarachnoid hemorrhage (Hunt and Hess I-III) on lidocaine infusion, with samples collected to measure plasma taurine concentration at various surgical times. Additionally, intracranial pressure would be measured, and both patient progression and prognosis would be evaluated.

Although various circumstances have prevented us from completing the above-mentioned protocol, we hope that other research groups can pursue our hypotheses and provide evidence to validate them.

Authors' contributions

I. Pérez-Neri contributed the original idea, review, and publication of the manuscript. L. Manrique-Carmona contributed the original idea and manuscript preparation.

Funding

This manuscript did not receive funding from any governmental, academic or commercial entity.

Conflicts of interest

I. Pérez-Neri is co-editor of *Archivos de Neurociencias*.

Ethical disclosures

Approval was obtained from L. Manrique-Carmona's family for the publication of this article.

References

1. Barges-Coll J, Pérez-Neri I, Avendaño J, Mendez-Rosito D, Gómez-Amador JL, Ríos C. Plasma taurine as a predictor of poor outcome in patients with mild neurological deficits after aneurysmal subarachnoid hemorrhage. J Neurosurg. 2013;119:1021-7.
2. Pérez-Neri I, Barges-Coll J, Ramírez-Bermúdez J, García-López R, Ojeda-López C, Méndez-Rosito D, et al. Taurina es un marcador de pronóstico, complicaciones y supervivencia de pacientes con diferentes trastornos neurológicos. Arch Neurocien. 2011;16(Supl II):22-4.
3. Manrique-Carmona LP, Pérez-Neri I. Pathophysiology and treatment of peritumoral brain edema: possible effect of lidocaine. Neurochemical Journal. 2018;12:9-14.

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ORIGINAL ARTICLE

Decreased GABBA$_A$ receptor β2 subunit immunoreactivity in a rat model of autism

Disminución de la inmunorreactividad a la subunidad β2 del receptor GABBA$_A$ en un modelo de autismo en ratas

*Ángel A. Puig-Lagunes[1], Frida S. Villada[2], Consuelo Morgado-Valle[2], Luis Beltran-Parrazal[2], Lizbeth D. Chi-Castañeda[2], and María L. López-Meraz[2]**

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Abstract

Background: *Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain, and activation of GABA type A (GABA$_A$) receptors mediates rapid inhibitory actions. Numerous studies have shown that individuals with autism spectrum disorder (ASD) exhibit abnormalities in the expression of GABA$_A$ receptors in several brain areas. In addition, animal models of ASD have suggested alterations in GABAergic neurotransmission and dysregulation of the balance between inhibitory and excitatory systems.* **Objective:** *We investigated the immunolabeling of GABBA$_A$ receptor β2 subunit (GARB2) in the hippocampus, the amygdala, and the thalamus of infant rats prenatally exposed to valproic acid (VPA) as a model of ASD.* **Methods:** *Pregnant female rats were injected with VPA (600 mg/Kg, i.p.) on embryonic day 12; control rats were injected with saline (SS group). On postnatal day 14, rats from both groups were anesthetized, transcardially perfused with 0.9% NaCl and 4% paraformaldehyde, and sequential coronal brain slices (40μm thickness) were obtained. Immunohistochemistry was performed to detect GARB2, and the relative optical density (OD) of immunoreactivity was analyzed.* **Results:** *Our data showed a statistically significant decrease in GARB2 immunoreactivity in the lateral amygdaloid nucleus and the ventral and lateral thalamic nuclei of VPA group when compared to the SS group. No statistically significant differences were found in the hippocampus.* **Conclusion:** *Our findings suggest that prenatal exposure to VPA reduces GARB2 immunoreactivity in limbic brain regions involved in social-emotional behavior, consistent with previous reports in individuals with ASD. These findings support for the involvement of the GABAergic system in the pathogenesis of ASD.*

Keywords: *Gamma-aminobutyric acid. GABA$_A$ receptor β2 subunit (GARB2). Autism. Valproic acid. Gamma-aminobutyric acid type A receptor.*

Resumen

Antecedentes: *El ácido gamma-aminobutírico (GABA) es el principal neurotransmisor inhibitorio del cerebro; la activación de los receptores GABA tipo A (GABA$_A$) media sus acciones inhibitorias rápidas. Los individuos con trastorno del espectro autista (TEA) presentan anomalías en la expresión de los receptores GABA$_A$ en diversas áreas cerebrales. Asimismo, modelos animales de TEA sugieren alteraciones en la neurotransmisión GABAérgica y una desregulación en el equilibrio entre los sistemas inhibitorios y excitatorios.* **Objetivo:** *Investigar la inmunoreactividad a la subunidad β2 del receptor GABA$_A$ (GARB2) en el hipocampo, la amígdala y el tálamo de ratas infantes expuestas prenatalmente a ácido valproico (AVP) como modelo de TEA.* **Método:** *Las hembras gestantes se inyectaron con AVP (600 mg/Kg, i.p. grupo AVP) durante el día embrionario 12;*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000018

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):67-73
www.archivosdeneurociencias.mx

las ratas control se inyectaron con salina (grupo SS). A los 14 días posnatales, las ratas de ambos grupos se perfundieron con NaCl 0.9% y paraformaldehído 4%, y se obtuvieron secciones cerebrales coronales (40µm de grosor). Se realizó inmunohistoquímica para detectar a GARB2. **Resultados:** *Se identificó una disminución de la inmunoreactividad a GARB2 en el núcleo amigdaloide lateral, así como en los núcleos talámicos ventral y lateral del grupo AVP en comparación con el grupo SS. No se detectaron diferencias en el hipocampo.* **Conclusión:** *Los hallazgos sugieren que la exposición prenatal al AVP reduce la inmunoreactividad de GARB2 en regiones cerebrales límbicas implicadas en comportamientos socio-emocionales, similar a informes previos en individuos con TEA. Nuestros resultados apoyan la implicación del sistema GABAérgico en la patogénesis del TEA.*

Palabras clave: *Ácido gamma-aminobutírico. Receptor $GABA_A$. Autismo. Ácido valproico. Subunidad β2 del receptor $GABA_A$ (GARB2).*

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopment disorder characterized by difficulties in social communication (verbal and nonverbal), interaction, and repetitive behaviors[1]. According to the Centers for Disease Control and Prevention in the United States, ASD affects 1 in 44 children, with a higher prevalence in boys than in girls (4.2 times more prevalent among boys)[2]. However, the etiology of ASD remains unclear.

Individuals with ASD often exhibit abnormalities in glutamate[3-6] and gamma-aminobutyric acid (GABA) neurotransmission systems[7-11]. GABA receptors type A ($GABA_A$) are ligand-gated ion channels that mediate rapid inhibition in the brain[12]. This receptor is composed of five protein subunits with different isoforms: α1-6, β1-3, γ1-3, δ, ε, θ, and π[13,14]. The most common arrangement of $GABA_A$ receptors in the central nervous system (20-50% of all central synapses) is the α1β2γ2[15,16], with GABA binding at the junction between α and β subunits[17]. Autoradiography studies of brain tissue from individuals with ASD have revealed a decrease density of $GABA_A$ and benzodiazepine receptors in the hippocampus and the anterior cingulate cortex[18-20]. In addition, reduced mRNA expression of $GABA_A$ receptor α6, β2, and γ2 subunits has been detected in the superior frontal cortex and the cerebellum of individuals with ASD[10]. Interestingly, the gene encoding the $GABA_A$ receptor β2 subunit has been associated with an increased risk of ASD[21]. Furthermore, 3-4% of individuals with ASD have chromosomal duplications in the proximal region of 15q11-q13, the most commonly observed chromosomal abnormality in these patients[22]. This chromosomal region contains the GABRB3, GABRA5, and GABRG3 genes, which encode β3, α5, and γ3 subunits of the $GABA_A$ receptor, respectively[23].

Preclinical studies using the ASD model based on VPA administration in rats have demonstrated disruptions in the excitatory/inhibitory balance in the amygdala[24], the hippocampus[25,26], and the cortex[27]. An impairment in GABA-mediated inhibition has been identified in the rat hippocampus in the VPA-induced model[27], as well as reduced $GABA_A$ receptor α1, α2, α3, and β3 mRNA levels in the medial prefrontal cortex of adult rodents[28]. Thus, evidence supports the hypothesis of GABAergic dysfunction in ASD. The VPA autism model has been widely used as an environmental model of ASD in rodents; however, the effect of prenatal exposure to VPA on brain $GABA_A$ receptor expression has not been fully characterized. In particular, the hippocampus, amygdala, and thalamus are brain areas involved in behavioral alterations or pathological changes observed in both individuals with ASD and animal models[29]. Therefore, we aimed to investigate the expression of the $GABA_A$ receptor β2 subunit (GARB2) in these brain areas in infant rats exposed to VPA *in utero.*

Methods

Animals

This study adhered to the Mexican guidelines on care and use of laboratory animals (NOM-062-ZOO-1999) and was approved by the Internal Committee for the Care and Use of Laboratory Animals of the Instituto de Investigaciones Cerebrales (CICUAL-CICE 2017-002-c). This study was carried out in strict accordance with the guide for the care and use of laboratory animals of the National Institutes of Health and under the ARRIVE guidelines. Wistar rats were obtained from our local colony and housed in our vivarium. Throughout the study, rats were maintained in a 12:12 hours light-dark cycle, with lights on at 08:00 hours, under room temperature and humidity conditions, with free access to water and food (Rismart). Adult female rats with regulated fertility cycles were mated overnight with a

sexually experienced male. The presence of spermatozoa in vaginal smears the following morning indicated the 1st day of pregnancy. On embryonic day 12.5, females received an intraperitoneal injection of 600 mg/kg of VPA (sodium valproate, Sigma-Aldrich, St. Louis, MO, dissolved in 0.9% NaCl for a concentration of 250 mg/mL) for the VPA group. Control rats were injected with 0.9% NaCl on the same embryonic day saline solution (SS) group. Females were housed individually and allowed to rear their litters[30]. Experiments to assess GARB2 immunoreactivity were performed on postnatal day 14 (P14) rat pups. The SS group consisted of 9 rats (3 males and 6 females), whereas the VPA group consisted of 10 rats (8 males and 2 females).

Immunohistochemistry

The rats were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and transcardially perfused with 0.9% NaCl, followed by 4% paraformaldehyde (prepared in 0.1 M phosphate buffer [PB], pH = 7.4) at a flow rate of 12 mL/min flow. Brains were left *in situ* overnight at 4°C. The next day, they were removed and postfixed in the same fixative for an additional 2 hours. Subsequently, the brains were cryoprotected with 30% sucrose (prepared in 0.1 M PB) for 72 hours at 4°C. Brain coronal sections (40 μm thick) were obtained at the level of the dorsal hippocampus using a Leica cryostat.

For the immunohistochemical detection, the slices were rinsed in 0.1M PB containing 0.1% triton (0.1% PBT). Endogenous peroxidases were quenched with 30% hydrogen peroxide for 10 min. To block nonspecific binding, the slices were treated with 5% horse serum in 0.3% PBT for 1 hour at room temperature. Subsequently, the slices were incubated with the primary antibody against GARB2 (1:1000; MAB341, Millipore) for 48 hours at 4°C. The slices were then incubated with a biotinylated anti-mouse secondary antibody (1:400; Vector Laboratories Inc.) for 90 min at room temperature, followed by incubation with the avidin-biotin complex (ABC kit PK-6100 Vector Laboratories Ellite-Standard Inc.) for an additional 90 min at room temperature. Immunodetection was visualized using 3,3′-diaminobenzidine in the presence of nickel (SK-4100 Vector Laboratories Inc.). Brain slices were mounted on electrostatically charged glass slides (Superfrost, Fisher Scientific) and coverslipped using non-aqueous medium (Permount, Fisher). Some brain sections were processed without using the primary antibody to rule out the presence of nonspecific labeling (negative control); no unwanted immunoreactivity was found.

Densitometric analysis

Photomicrographs of three different brain sections per rat (from either the left or right hemisphere) were taken using a Leica DM500 light microscope connected to a Leica ICC50 HD digital camera. The Leica Application System LAS EZ 4.8 software was used for this purpose. Photomicrographs were taken of the dorsal hippocampus (including the strata oriens, pyramidal, and radiatum in CA1, CA2, and CA3 fields, as well as the granule cell layer and hilus of the dentate gyrus), the lateral and basolateral nuclei of the amygdala, and the ventral and lateral nuclei of the thalamus. A standard brightness of 55% and a magnification of ×40 were used.

The relative optical density (OD) of GARB2 immunoreactivity was analyzed using Fiji Image J software. The software was calibrated according to the develo-per's instructions, allowing the transformation of pixel values to a scale that correlates with OD. This allowed the determination of the mean gray value of the region of interest (ROI)[31]. The ROI was defined as 6,500 μm^2 for each stratum of the hippocampus and 70,000 μm^2 for both the amygdala and the thalamus. The presence of immunoreactivity to GARB2 was observed as gray to black, whereas its absence was indicated by a white color. The OD background was determined by avera-ging the OD of the corpus callosum from the slices used. This brain region was chosen because it does not contain $GABA_A$ receptors[32]. The background was then subtracted from all images. The final GARB2 OD for each animal was obtained by averaging the OD from the three analyzed slices and expressed as arbitrary units. A higher relative OD indicates increased expression of the protein of interest.

Statistical analysis

Data initially followed a normal distribution using the Shapiro–Wilk test. Differences in GARB2 immunoreactivity between the VPA and SS groups in different brain regions were analyzed using either an unpaired two-tailed Student's t-test or a Mann–Whitney test, as appropriate. Analyses were performed using GraphPad Prism software (version 6), with a significance level of $\alpha = 0.05$.

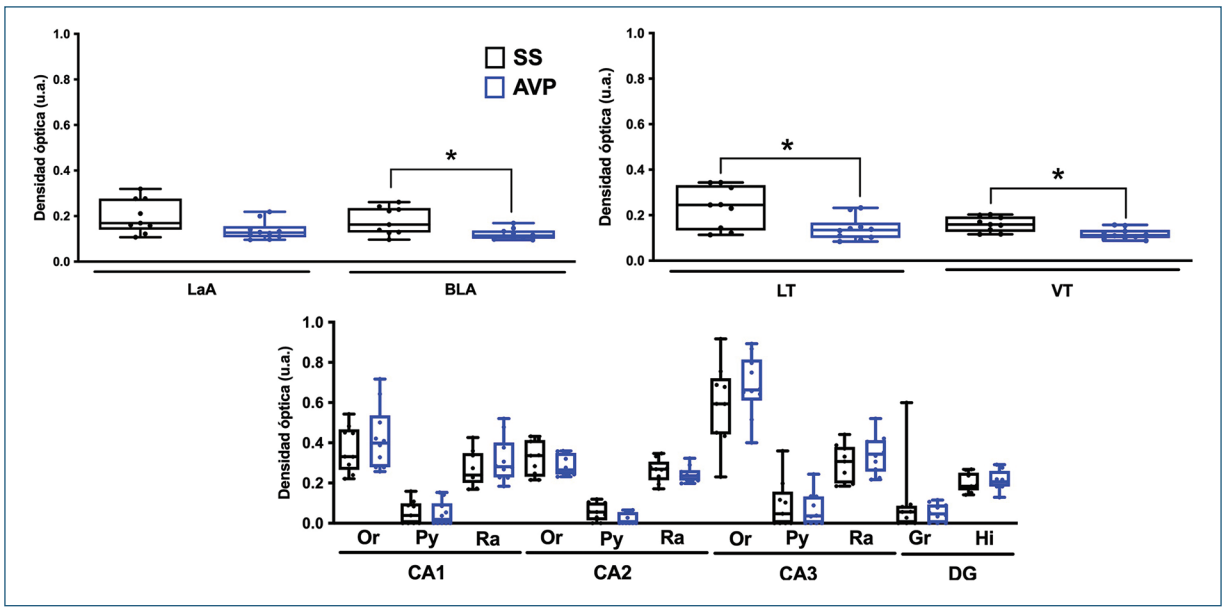

Figure 1. Effect of prenatal exposure to valproic acid on $GABA_A$ receptor β2 subunit immunoreactivity in the amygdala, thalamus, and hippocampus of postnatal day 14 rat pups. SS: saline solution; LaA: lateral nucleus of the amygdala; BLA: basolateral nucleus of the amygdala; LT: lateral nucleus of the thalamus; VT: ventral nucleus of the thalamus; Or: oriens; Py: pyramidale; Ra: radiatum; DG: Dentate gyrus; Gr: Granular layer, Hi: Hilus; CA1, CA2, and CA3 hippocampal regions. *p < 0.05.

Results

Statistical analysis showed that prenatal VPA administration significantly decreased GARB2 immunoreactivity in the basolateral nucleus of the amygdala (t = 2.814, df = 17; p = 0.012) compared to the SS group. A non-significant reduction was also observed in the lateral amygdaloid nucleus (MWU = 21; p = 0.0534). Similarly, VPA-treated rats exhibited lower OD values, reflecting reduced GARB2 immunoreactivity in both the lateral (t = 2.804, df = 17; p = 0.0122) and ventral (t = 3.281, df = 17; p < 0.004) thalamic nuclei compared to SS group. No significant differences were found between VPA and SS groups in any hippocampal subregions or strata (p > 0.05), although a trend toward decreased GARB2 immunoreactivity was observed in the CA2 pyramidal layer (MWU = 23.5; p = 0.07; Figs. 1 and 2).

Discussion

One hypothesis proposed to explain the etiology of ASD is the imbalance between neuronal excitation and inhibition, primarily mediated by glutamate and GABA, respectively[33]. In this study, we found that infant rats prenatally exposed to VPA exhibited reduced GARB2 immunoreactivity in specific regions of the amygdala and thalamus compared to control rats. These preclinical results support the relevance of GABA receptors in the pathophysiology of autism.

Several studies have reported a decrease in GABA levels in the frontal lobe and anterior cortex of patients with ASD[11,34] and decreased levels of glutamic acid decarboxylase 65 and 67, the enzyme that catalyzes the conversion of glutamate to GABA, in the parietal cortex and cerebellum of *post-mortem* samples from adults with ASD[8,35], and in the hippocampus and cerebellum of VPA-exposed rats[36]. With respect to GABA receptors, lower densities of $GABA_A$ receptors have been found in the hippocampus, anterior and posterior cingulate cortex, and fusiform gyrus of *post-mortem* brain tissue from individuals with autism[18-20]. A decrease in GARB2 protein levels has also been observed in the superior frontal cortex and downregulation of its mRNA in the cerebellum[10]. Interestingly, GARB2 polymorphisms have also been associated with ASD[21]. A (123) I-iomazenil (IMZ, a ligand from the benzodiazepine receptor) single-photon emission computed tomography study in children with ASD found decreased accumulation of (123) I-IMZ in the middle and superior frontal cortex[37]. However, a more recent study found no

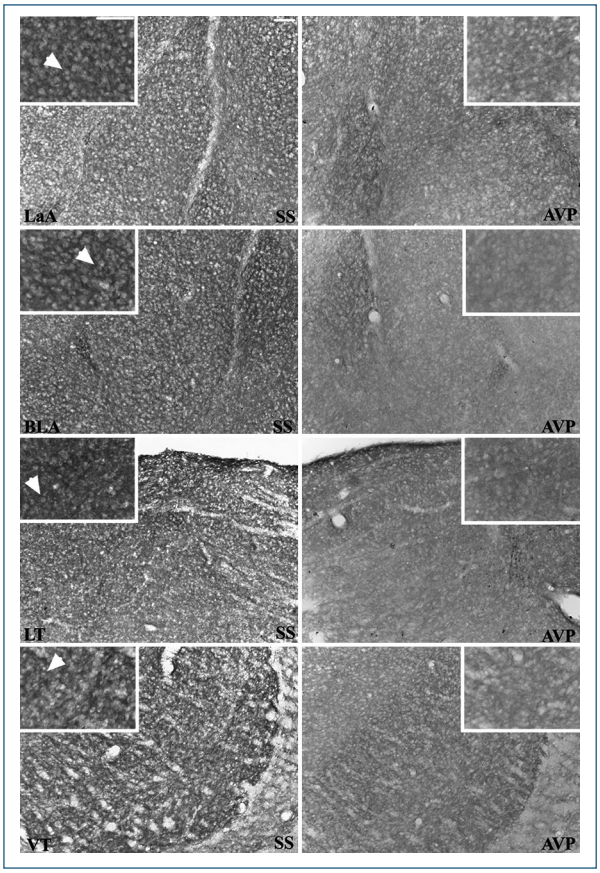

Figure 2. Photomicrographs show $GABA_A$ receptor β2 subunit immunoreactivity in the amygdala and thalamus of a postnatal day 14 rat pup exposed *in utero* to valproic acid (VPA) or saline solution (SS). The insets show greater GARB2 immunoreactivity in the rat from the SS group than in the rat from the VPA group (scale bars = 100 μm). Arrowheads point to GARB2 immunoreactive cells. LaA: lateral nucleus of the amygdala; BLA: basolateral nucleus of the amygdala; LT: lateral nucleus of the thalamus; VT: ventral nucleus of the thalamus.

changes in $GABA_A$ receptor or $GABA_A$ α5 subunit availability in the hippocampal or amygdala regions of adults with ASD[33].

Our results showed that infant rats prenatally exposed to VPA displayed decreased GARB2 immunoreactivity in the amygdala and thalamus compared to age-matched rats with standard gestation. These findings align with the excitation/inhibition imbalance hypothesis in individuals with ASD. Reduced expression of GARB2, which indirectly indicates reduced availability of $GABA_A$ receptors, may contribute to social deficits[25,38,39], and other neurological changes observed in the VPA rat model, such as increased seizure susceptibility[25,30]. The gene encoding GARB2 has been previously associated with a higher risk of ASD[21]. It is noteworthy that both the amygdala and thalamus have been implicated in behavioral alterations and pathological changes observed in individuals with ASD and animal models[25,29].

Consisted with our findings, Yang et al[28]. also described impaired inhibitory GABAergic neurotransmission due to decreased GABA release and mRNA levels of $GABA_A$ receptor α1, α2, α3, and β3 subunits in the medial prefrontal cortex of VPA-exposed mice. These authors also demonstrated that acute administration of combined $GABA_A$ and $GABA_B$ receptor agonists reduced deficits in sociability, anxiety, and repetitive behaviors in this ASD model[28]. However, Bertelsen et al[40]. reported increased binding of [11C] Ro15-4513 (an agonist with high affinity for the $GABA_A$ receptor α-subunit) in the left amygdala of VPA-treated rats as an ASD model, whereas no significant differences were found in the thalamus compared to control rats. That study differs from ours in the VPA administration protocol and receptor detection methodology. They administered 20 mg/kg of VPA daily during pregnancy, whereas we injected a single dose of 600 mg/kg on embryonic day 12. Therefore, it is essential to consider potential differences in the assessed neurobiological changes depending on the methodological procedures used. A study using other ASD mouse models (Cntnap2 or Shank3 knockout mice and mice with the 16p11.2 deletion) did not identify differences in the levels of $GABA_A$ receptors or their α5 subunit in the frontal cortex, cingulate cortex, caudate/putamen, dorsal hippocampus, cerebellum, or amygdala between these three models or compared to control mice[35]. This discrepancy may be due to specific changes in $GABA_A$ receptor subunits or the different etiology of the ASD models (i.e., environmental versus genetic). Additional experimental protocols are needed to better understand the complex neurobiology of ASD.

Conclusions

Our study provides further evidence supporting the role of GABAergic dysfunction, specifically GARB2 expression, in the pathophysiology of ASD using a VPA-induced rat model. Our findings indicate that prenatal VPA exposure leads to reduced GARB2 immunoreactivity in the amygdala and thalamus, regions associated with social deficits, and other neurological alterations in ASD. These findings are consistent with the hypothesis of an excitation/inhibition imbalance in

individuals with ASD. However, the complex neurobiology of ASD warrants further investigation to elucidate the contributions of specific $GABA_A$ receptor subunits and the varying etiologies of ASD models. A deeper understanding of the role of the GABAergic system in ASD, including the impact of hippocampal GABAergic receptors, could contribute to the search of novel therapeutic interventions and help improve the quality of life for individuals with ASD.

Author's contributions

MLLM contributed to the study conceptualization and design, material preparation, and provided study resources. The first draft of the manuscript was written by AAPL. FSV and AAPL performed the experiments and contributed to data acquisition and analysis. LDCC, CMV, and LBP provided study resources and contributed to writing review and editing. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This research did not receive donations from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of persons and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that no patient data appear in this article. In addition, the authors have acknowledged and followed the recommendations according to the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables or their corresponding captions or legends.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: APA Press; 2013.
2. Maenner MJ, Shaw KA, Bakian AV, Bilder DA, Durkin MS, Esler A, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 Sites, United States, 2018. MMWR Surveill Summ. 2021;70:1-16.
3. Hassan TH, Abdelrahman HM, Abdel Fattah NR, El-Masry NM, Hashim HM, El-Gerby KM, et al. Blood and brain glutamate levels in children with autistic disorder. Res Autism Spectr Disord. 2013;7:541-8.
4. Page LA, Daly E, Schmitz N, Simmons A, Toal F, Deeley Q, et al. *In vivo* 1H-magnetic resonance spectroscopy study of amygdala-hippocampal and parietal regions in autism. Am J Psychiatry. 2006;163:2189-92.
5. Shinohe A, Hashimoto K, Nakamura K, Tsujii M, Iwata Y, Tsuchiya KJ, et al. Increased serum levels of glutamate in adult patients with autism. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:1472-7.
6. Shimmura C, Suda S, Tsuchiya KJ, Hashimoto K, Ohno K, Matsuzaki H, et al. Alteration of plasma glutamate and glutamine levels in children with high-functioning autism. PLoS One. 2011;6:e25340.
7. Ansary El, Ayadhi Al. GABAergic/glutamatergic imbalance relative to excessive neuroinflammation in autism spectrum disorders. J Neuroinflammation. 2014;11:1-189.
8. Fatemi SH, Halt A, Stary J, Kanodia R, Schulz SC, Realmuto G. Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices of autistic subjects. Biol Psychiatry. 2002;52:805-10.
9. Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD. GABA(A) receptor downregulation in brains of subjects with autism. J Autism Dev Disord. 2009;39:223-30.
10. Fatemi SH, Reutiman TJ, Folsom TD, Rustan OG, Rooney RJ, Thuras PD. Downregulation of GABAA receptor protein subunits α6, β2, δ, ε, γ2, θ, and ρ2 in superior frontal cortex of subjects with Autism. J Autism Dev Disord. 2014;44:1833-45.
11. Harada M, Taki MM, Nose Y, Kubo H, Mori K, Nishitani H, et al. Non-invasive evaluation of the GABAergic/glutamatergic system in autistic patients observed by MEGA-editing proton MR spectroscopy using a clinical 3 tesla instrument. J Autism Dev Disord. 2011;41:447-54.
12. Bormann J. The 'ABC' of GABA receptors. Trends Pharmacol Sci. 2000;21:16-9.
13. Olsen RW, Sieghart W. International union of pharmacology. LXX. Subtypes of gamma-aminobutyric acid(A) receptors: classification on the basis of subunit composition, pharmacology, and function. Update. Pharmacol Rev. 2008;60:243-60.
14. Olsen RW, Sieghart W. GABA A receptors: subtypes provide diversity of function and pharmacology. Neuropharmacology. 2009;56:141-8.
15. Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience. 2000;101:815-50.
16. Nutt D. GABAA receptors: subtypes, regional distribution, and function. J Clin Sleep Med. 2006;2:S7-11.
17. Whiting PJ, Bonnert TP, McKernan RM, Farrar S, Le Bourdellès B, Heavens RP, et al. Molecular and functional diversity of the expanding GABA-A receptor gene family. Ann N Y Acad Sci. 1999;868:645-53.
18. Blatt GJ, Fitzgerald CM, Guptill JT, Booker AB, Kemper TL, Bauman ML. Density and distribution of hippocampal neurotransmitter receptors in autism: an autoradiographic study. J Autism Dev Disord. 2001;31:537-43.
19. Oblak A, Gibbs TT, Blatt GJ. Decreased GABAA receptors and benzodiazepine binding sites in the anterior cingulate cortex in autism. Autism Res. 2009;2:205-19.
20. Oblak AL, Gibbs T, Blatt GJ. Reduced GABAA receptors and benzodiazepine binding sites in the posterior cingulate cortex and fusiform gyrus in autism. Brain Res. 2011;1380:218-28.
21. Ma DQ, Whitehead PL, Menold MM, Martin ER, Ashley-Koch AE, Mei H, et al. Identification of significant association and gene-gene interaction of GABA receptor subunit genes in autism. Am J Hum Genet. 2005;77:377-88.
22. Lamb J, Moore J, Bailey A, Monaco AP. Autism: recent molecular genetic advances. Hum Mol Genet. 2000;9:861-8.
23. Bettler B, Kaupmann K, Mosbacher J, Gassmann M. Molecular structure and physiological functions of GABA(B) receptors. Physiol Rev. 2004;84:835-67.
24. Lin HC, Gean PW, Wang CC, Chan YH, Chen PS. The amygdala excitatory/inhibitory balance in a valproate-induced rat autism model. PLoS One. 2013;8:e55248.

25. Kim KC, Kim P, Go HS, Choi CS, Park JH, Kim HJ, et al. Male-specific alteration in excitatory post-synaptic development and social interaction in pre-natal valproic acid exposure model of autism spectrum disorder. J Neurochem. 2013;124:832-43.
26. Bristot Silvestrin R, Bambini-Junior V, Galland F, Daniele Bobermim L, Quincozes-Santos A, Torres Abib R, et al. Animal model of autism induced by prenatal exposure to valproate: altered glutamate metabolism in the hippocampus. Brain Res. 2013;1495:52-60.
27. Banerjee A, García-Oscos F, Roychowdhury S, Galindo LC, Hall S, Kilgard MP, et al. Impairment of cortical GABAergic synaptic transmission in an environmental rat model of autism. Int J Neuropsychopharmacol. 2013;16:1309-18.
28. Yang JQ, Yang CH, Yin BQ. Combined the GABA-A and GABA-B receptor agonists attenuates autistic behaviors in a prenatal valproic acid-induced mouse model of autism. Behav Brain Res. 2021;403:113094.
29. Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends Neurosci. 2008;31:137-45.
30. Puig-Lagunes AA, Manzo J, Beltrán-Parrazal L, Morgado-Valle C, Toledo-Cárdenas R, López-Meraz ML. Pentylenetetrazole-induced seizures in developing rats prenatally exposed to valproic acid. PeerJ. 2016; 4:e2709.
31. Rasband WS. ImageJ. Bethesda, Maryland, USA: U.S. National Institutes of Health; 1997-2018. Available from: https://imagej.nih.gov/ij
32. Richards JG, Schoch P, Haring P, Takacs B, Möhler H. Resolving GABA/benzodiazepine receptors: cellular and subcellular localization in the CNS with monoclonal antibodies. J Neurosci. 1987;7:1866-6.
33. Horder J, Petrinovic MM, Mendez MA, Bruns A, Takumi T, Spooren W, et al. Glutamate and GABA in autism spectrum disorder-a translational magnetic resonance spectroscopy study in man and rodent models. Transl Psychiatry. 2018;8:106.
34. Cochran DM, Sikoglu EM, Hodge SM, Edden RA, Foley A, Kennedy DN, et al. Relationship among glutamine, γ-aminobutyric acid, and social cognition in autism spectrum disorders. J Child Adolesc Psychopharmacol. 2015;25:314-22.
35. Horder J, Andersson M, Mendez MA, Singh N, Tangen Ä, Lundberg J, et al. $GABA_A$ receptor availability is not altered in adults with autism spectrum disorder or in mouse models. Sci Transl Med. 2018;10:eaam8434.
36. Hou Q, Wang Y, Li Y, Chen D, Yang F, Wang S. A developmental study of abnormal behaviors and altered GABAergic signaling in the VPA-treated rat model of autism. Front Behav Neurosci. 2018;12:182.
37. Mori T, Mori K, Fujii E, Toda Y, Miyazaki M, Harada M, et al. Evaluation of the GABAergic nervous system in autistic brain: (123)I-iomazenil SPECT study. Brain Dev. 2021;34:648-54.
38. Bambini-Junior V, Rodrigues L, Behr GA, Moreira JC, Riesgo R, Gottfried C. Animal model of autism induced by prenatal exposure to valproate: behavioral changes and liver parameters. Brain Res. 2011;1408:8-16.
39. Schneider T, Przewłocki R. Behavioral alterations in rats prenatally exposed to valproic acid: animal model of autism. Neuropsychopharmacology. 2005;30:80-9.
40. Bertelsen F, Møller A, Folloni D, Drasbek KR, Scheel-Krüger J, Landau AM. Increased $GABA_A$ receptor binding in amygdala after prenatal administration of valproic acid to rats. Acta Neuropsychiatr. 2017;29:309-14.

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ORIGINAL ARTICLE

Risk factors for the development of impulse control disorders in Mexican subjects with Parkinson's disease

Factores de riesgo para el desarrollo de trastornos del control de impulsos en sujetos mexicanos con enfermedad de Parkinson

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Abstract

Background: *Impulse control disorders (ICDs) are behaviors that are performed repeatedly to the point of interfering with the patient's functionality and daily life, without regard for their consequences and with the sole purpose of obtaining immediate gratification. ICDs have been related to dopaminergic treatment.* **Objective:** *To analyze the association of different risk factors for the development of ICD in the Mexican population.* **Methods:** *A cross-sectional study was carried out. The data collected affects the years 2021 to 2023. Data were collected through structured interviews including age, gender, year of symptom onset, year of diagnosis, levodopa equivalent dose, and antiparkinsonian treatment, and history of smoking and alcohol use was evaluated.* **Results:** *A total of 244 patients diagnosed with Parkinson's disease (PD) were included, of whom 146 (59.8%) were men and 98 (40.2%) were women. The mean age was 63 ± 12.10 years. A total of 35 (14.3%) patients with ICD (ICD-PD) were found; the non-ICD group included 209 subjects (85.7%). When analyzing antiparkinsonian drugs, a higher use of dopamine agonists was found in the ICD group but did not reach statistical significance (p = 0.078). Only the variable alcoholism was identified as a risk factor in the logistic regression, as can be seen in its p = 0.034, the odds ratio value IS 2.55, indicating that patients with alcoholism have a 2.5 times higher risk of developing ICD. The rest of the variables did not show statistically significant p-values.* **Conclusion:** *History of alcohol use was the main associated risk factor with the development of ICD.*

Keywords: *Parkinson's disease. Impulse control disorder. Risk factors.*

Resumen

Antecedentes: *Los trastornos de control de impulsos (TCI) son comportamientos que se realizan repetidamente hasta interferir con la funcionalidad y la vida diaria del paciente, sin considerar sus consecuencias y con el único propósito de obtener gratificación inmediata. Los TCI han sido relacionados con el tratamiento dopaminérgico.* **Objetivo:** *Analizar la asociación de diferentes factores de riesgo para el desarrollo de TCI en la población mexicana.* **Métodos:** *Se llevó a cabo un estudio transversal. Los datos recolectados corresponden a los años 2021 a 2023. Se recopiló información a través de entrevistas*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000019

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):74-79
www.archivosdeneurociencias.mx

estructuradas que incluyeron edad, sexo, año de inicio de los síntomas, año del diagnóstico, dosis equivalente de levodopa, tratamiento antiparkinsoniano y antecedentes de consumo de tabaco y alcohol. **Resultados:** *Se incluyeron 244 pacientes diagnosticados de enfermedad de Parkinson (EP), de los cuales 146 (59.8%) eran hombres y 98 (40.2%) eran mujeres. La edad media fue de 63 ± 12.10 años. Se identificaron 35 (14.3%) pacientes con TCI (TCI-EP); el grupo sin TCI incluyó 209 sujetos (85.7%). Al analizar los fármacos antiparkinsonianos se encontró un mayor uso de agonistas de la dopamina en el grupo con TCI, aunque no alcanzó significancia estadística (p = 0.078). Solo el antecedente de alcoholismo fue identificado como factor de riesgo en la regresión logística, con p = 0.034 y una odds ratio de 2.55, lo que indica que los pacientes con alcoholismo tienen 2.5 veces más riesgo de desarrollar TCI. El resto de las variables no mostraron valores de p estadísticamente significativos*. **Conclusiones:** *El consumo previo de alcohol fue el principal factor de riesgo asociado con el desarrollo de TCI.*

Palabras clave: *Enfermedad de Parkinson. Trastorno de control de impulsos. Factores de riesgo.*

Introduction

Parkinson's disease (PD) is a complex, adult-onset neurodegenerative process being the second most common neurodegenerative disease after Alzheimer's disease[1]. Neuronal loss in the substantia nigra, which causes striatal dopamine (DA) deficiency, and intracellular inclusions containing aggregates of α-synuclein, are the neuropathological hallmarks of PD[2].

Although there is currently no treatment that halts the progression of PD, current treatment aims to improve symptoms by (a) replacing DA with its precursor and (b) inhibiting of the enzymes that break down DA[3].

A group of symptoms in PD are non-motoric[4], such as sleep disorders, cognitive disorders, and mood disorders[5,6].

Impulse control disorders (ICDs) and related impulsive and compulsive behaviors have been increasingly recognized in the context of PD and have been mainly related to dopaminergic treatment[7].

According to published literature, 10% of the overall population with PD meets the criteria for at least one episode of ICD in their life[8].

ICDs are behaviors that are carried out repeatedly, excessively, and compulsively to the extent that they interfere with the patient's functionality and daily life, regardless of their consequences, and solely for the purpose of immediate gratification. Their severity can vary, ranging from a mild change in behavior noticed by the patient and their family without functional implications and even improving their quality of life to a major problem that involves economic ruin, legal issues, job loss, divorce, or health risks. Among other risk factors, a personal history of alcoholism or smoking, male gender, and early-onset age is found[9].

ICDs are more common in patients with PD than in the general population. They are related to treatment with dopaminergic agonists as they increase the risk by 2-3.5 times with an average time between starting the medication and the presence of ICDs being 23 months[10].

ICDs are not typically spontaneously reported by the patient which is why inquiring about these symptoms may be the only way to detect and manage a serious socio-familial problem[11].

Objective

To determine the frequency of known risk factors for ICD in Mexican patients with PD.

Methods

A cross-sectional study of patients diagnosed with PD according to the Movement Disorders Society (MDS) criteria[12] was conducted at the National Institute of Neurology and Neurosurgery in the Movement Disorders Clinic. The collected data ranged from 2021 to 2023 and were obtained through a structured interview including variables such as age, gender, year of symptom onset, year of diagnosis, socioeconomic status, equivalent levodopa dose (LD), dopaminergic medications including LD, DA, amantadine, and monoamine oxidase type B inhibitors (MAOi´s) to directly compare different antiparkinsonian treatment doses[13]. The presence or absence of smoking (defined for our study as regular tobacco consumption) or alcohol use (defined for our study as regular alcohol intake) was evaluated and MDS-Unified PD Rating Scale item 1.6 on dopaminergic dysregulation was taken as a nominal variable[14] indicating whether it was present or not.

Smoking habit was operationally defined as follows: categorization of an individual as a current smoker, former smoker, or never smoker, based on self-report or clinical assessment. Secondhand smoke exposure

Table 1. Sociodemographic data of the sample between groups

Variable	ICD-PD		Non ICD-PD		p
	Mean	Standard deviation	Mean	Standard deviation	
Age	61.51	11.763	63.30	12.171	0.420
Gender	0.34	0.487	0.41	0.493	0.445
Disease duration	7.66	4.814	7.33	5.330	0.734
Years of education	12.86	5.359	10.26	5.206	0.011
H and Y	2.20	0.719	2.37	0.787	0.200
Age of onset of symptoms	52.46	11.840	54.42	13.447	0.418
Age of diagnosis	54.40	11.790	56.37	13.134	0.405

ICD: impulse control disorder; ICD-PD: impulse control disorder Parkinson's disease.

is the extent to which an individual is exposed to smoke from others who smoke.

The operational definition for alcohol intake included: the characterization of an individual's drinking habits such as moderate, heavy, or occasional drinking. Alcohol dependency or alcohol use disorder was defined as the presence and severity of symptoms associated with alcohol dependency using standardized diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

All subjects were evaluated by a neurologist specialized in movement disorders. Subjects were divided into two groups according to ICD presence: the ICD-PD group and non-ICD group.

The presence of ICDs was assessed using the questionnaire for impulsive-compulsive disorders (QUIP-RS). The QUIP-RS is a brief, self-reported, or rater-administered rating scale to assess the frequency and severity of ICD symptoms and related behaviors reported to occur in PD[15] and it was evaluated as a nominal variable by having a point on the scale considering it as a positive result for the presence of this diagnosis. It will be analyzed as a nominal variable to determine the number of patients who reported self-perceived impulsive behavior at the time of application of the scale if they presented behaviors.

Levodopa equivalent daily dose was calculated as published elsewhere[13].

Statistical analysis

A normality test was performed resulting in a non-normal distribution. Consequently, the statistical test, used for the nominal variables, was chi-square, while quantitative variables were analyzed using the Mann–Whitney U-test.

To investigate the relationship between the presence or absence of ICDs and known risk factors, potential confounding variables were added to a logistic regression model as independent variables. These included age, sex, history of drug abuse, and smoking and disease duration. The odds ratio (OR) is a measure commonly used in statistics and epidemiology to quantify the strength and direction of the association between two variables, particularly in the context of case-control studies. An OR > 1 indicates an increased odds of an event occurring, while an OR < 1 indicates a decreased odd.

The study has been reviewed and approved by the Institutional Review Board and has been found to be in compliance with all relevant ethical guidelines and standards for research involving human participants. All subjects gave informed consent.

Results

A total of 244 patients diagnosed with PD were included, of whom 146 (59.8%) were men and 98 (40.2%). Table 1 shows the sociodemographic data of our patients in more detail.

A total of 35 (14.3%) patients with ICD (ICD-PD) were found; the non-ICD group included 209 subjects (85.7%).

When analyzing antiparkinsonian drugs, a higher use of DA agonists was found in the ICD group but did not reach statistical significance (p = 0.078). More detailed information on drug intake is shown in table 2.

Table 2. Comparison of the main demographic and clinical characteristics between patients with and without ICD

Variable	ICD-PD (n = 35) (%)	Non-ICD-PD (n = 189)	p
Gender (male)	23 (65.7)	123 (65)	0.283
Use of amantadine	6 (17.1)	23 (12.1)	0.221
Smoking history	10 (28.5)	54 (28.6)	0.438
Alcohol intake history	16 (45.7)	55 (29.1)	0.019
Use of levodopa	35 (100)	189 (100)	0.175
Use of dopamine agonist	20 (57.1)	89 (47.1)	0.078
Use of MAOi	4 (11.4)	38 (20)	0.236

ICD: impulse control disorder; PD: Parkinson's disease; MAOi: monoamine oxidase inhibitor.

Table 3. Comparison of the main demographic and clinical characteristics using logistic regression

Variable	OR	95% Confidence interval	p
MAOi	0.488	0.154-1.549	0.223
Dopaminergic Agonist	1.888	0.847-4.210	0.120
Amantadine	2.006	0.687-5.855	0.203
Gender (female)	0.885	0.381-2.055	0.776
Alcoholism	2.551	1.07-6.070	0.034
Smoking	0.889	0.361-2.690	0.798
Disease duration	0.991	0.910-1.079	0.838
LEDD	1.000	0.999-1.000	0.956
Age	0.985	0.956-1.016	0.350

LEDD: levodopa equivalent daily dose; MAOi: monoamine oxidase inhibitor; OR: odds ratio.

Regarding smoking habits, no statistically significant differences were found between the ICD-PD and non-ICD groups (p = 0.73).

Regarding the use of alcohol in ICD-PD, a statistically significant difference was found (p = 0.019).

No statistically significant difference was found between groups regarding age at diagnosis, age at symptom onset, age, diagnostic delay, and levodopa equivalent doses.

A logistic regression using the following variables independent levodopa intake, MAOi´s, dopaminergic agonists, amantadine, gender, alcoholism, and smoking was carried out. The presence of ICD was the dependent variable.

Only the variable alcoholism was identified as a risk factor, as can be seen in its p = 0.034, the OR value is 2.551, indicating that patients with alcoholism have a 2.5 times higher risk of developing ICD in comparison to the other group. The 95% confidence interval provides a range of values within which we can be 95% confident that the true OR lies. In this case, the interval spans from 1.07 to 6.070; the interval does not include 1 which suggests statistical significance. Finally, the p-value was 0.034, which is < 0.05, suggesting that the association between the variables is statistically significant.

The rest of the variables gave us a p-value that does not show statistical significance in its association with ICD. More details are shown in table 3.

Discussion

The DSM-IV defines ICDs as the inability to resist an impulse, attraction, or temptation to perform an act that ends up being harmful to the individual or their environment. It includes alterations in sexual behavior, pathological gambling, compulsive shopping, bulimic episodes, and compulsive medication consumption[16]. On the other hand, the term "impulsivity" describes a pattern of behaviors based on hasty decisions, without considering potential adverse consequences[17].

Conventionally four types of behaviors have been recognized and classified as ICDs, namely hypersexuality, compulsive buying, pathological gambling, and compulsive food intake also known as binge eating disorder[18].

Considering the nature of ICDs, it has recently been subdivided into two main processes linked to different neural networks and activated by different experimental paradigms: cognitive impulsivity and motor impulsivity. ICDs have been conceptualized as "behavioral addictions"[1] because of their similarities to substance use disorders, with which they share risk factors, clinical features, cognitive changes, neurobiological substrates, and treatments. The term "impulse control disorders" covers the four major ICDs that occur in Parkinson´s disease, and "related behaviors" refers to other behaviors[19].

Variables associated with ICDs include a personal or family history of alcohol use disorder or pathological gambling, impulsive or novelty-seeking traits, younger age, and male gender[20]. In some studies, the prognosis of ICDs was better in women than in men,[21] early onset of PD, being single, and having smoked or smoked

cigarettes[22]. According to what has been described in the literature on our study population, there is a relationship between alcohol and ICD.

Younger patients are more likely to be treated with a dopaminergic agonist; the effect of age was maintained after controlling for dopaminergic agonist exposure[23]; however, in our study, such association was not found.

Chronic dopaminergic treatment can induce motor and non-motor side effects, mainly DIL and CDI. In fact, the incidence of ICD has been increasingly recognized in recent years; it has been suggested that this is pro-bably related to the increased use of dopaminergic agonists[24].

The association of ICDs in PD with treatment with DA agonists has been studied and this association depends on the dose and is similar in the entire class of DA agonists[25]. In the present study, only a trend was found without reaching a statistically significant difference.

Use of alcohol has been frequently associated with impulse control problems due to hypoactive function and disrupted network connectivity in regions involving the ventromedial prefrontal cortex, caudate, and left lateral/dorsolateral prefrontal cortex underlies stress-related impulse control difficulties in alcohol-dependent patients[26]. Alcohol use was the only statistically signi-ficant risk factor found in our study.

ICD is associated with poor quality of life of the patient and their caregivers, as well as delinquent behaviors, so its timely detection and management is important[27]. ICD may also function as a coping strategy for the existential and personal crises that often follow the diagnosis of chronic disease[28]. Screening is not always straightforward in clinical practice as it relies on the self-assessment of PwP who may lack insight into the frequency, severity and consequences of their own behavior[29]; because of this, doctors must carefully eva-luate patients with maladaptive behaviors[30].

There are several possible reasons why one study may fail to show an association between age and ICDs, even though other studies have reported such association. Here are some factors to consider: (1) sample size, if the study with no observed association has a smaller sample size compared to the studies that found an association, it may not have had enough statistical power to detect the effect. In smaller samples, random variations can have a more significant impact on the results; (2) Study design, design, and methodology can greatly influence the outcomes. Different studies may use different research designs (cross-sectional, longitudinal, case-control, etc.) and data collection methods which can lead to varying results; (3) differences in the characteristics of the study populations can play a significant role. If the study with no association focused on a population with unique characteristics or risk factors it may not be directly comparable to other studies. Factors such as cultural, genetic, or socioeconomic differences can influence the prevalence of ICDs; and (4) random chance, sometimes, even in well-designed studies, results can appear due to random chance. This is more likely to occur in smaller studies but can still happen in larger ones.

An additional factor to consider is the period. ICD may have varying prevalence rates across different time periods. A study conducted at a particular point in time may not reflect the current state of the population's ICDs, especially when risk factors are already known and accounted for when choosing an antiparkinsonian drug or dose.

Finally, alcohol frequency (number of days per week or per month an individual consumes alcoholic beverages) or alcohol quantity (amount of alcohol consumed on each occasion expressed in standard drink units) was not assessed. Future studies should include these variables.

Conclusion

With this study, our objective was to identify the various risk factors for the development of ICDs in the Mexican population. The prevalence of ICD was within the numbers reported in the literature. Nevertheless, among the known risk factors, only alcohol use was statistically related to ICDs.

Authors' contributions

Luisa Guadalupe Lira-Juárez: conceptualization, data curation, formal analysis, writing - original draft. Ariadna Domínguez-García: data curation. Andrés Yamil Regalado-Mustafá: data curation. Elba Citlali Santiago-de la Cruz: data curation. María de los Ángeles Guadalupe Medrano-Delgado: data curation. Ana Jimena Hernández-Medrano: writing - original draft. Giovanni Elivt De La Rosa-Patlan: data curation. Mayela Rodríguez-Violante: monitoring, validation, visualization. Amin Cervantes-Arriaga: project administration, formal analysis.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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

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

References

1. Martínez-Fernández R, Gasca-Salas CC, Sánchez-Ferro A, Obeso JA. Actualización en la enfermedad de Parkinson. Rev Méd Clín Las Condes. 2016;27:363-79.
2. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3:17013.
3. Chávez-León E, Ontiveros-Uribe MP, Carrillo-Ruiz JD. La enfermedad de Parkinson: neurología para psiquiatras. Salud Ment. 2013;36:315-24.
4. Daniel SM, Hans CV, Melissa IQ, Manuela GC. Parkinson disease: pathophysiology, diagnosis and treatment. Rev Univ Ind Santander Salud. 2018;50:79-92.
5. Berganzo K, Tijero B, González-Eizaguirre A, Somme J, Lezcano E, Gabilondo I, et al. Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups. Neurologia. 2016;31:585-91.
6. Bhat S, Acharya UR, Hagiwara Y, Dadmehr N, Adeli H. Parkinson's disease: cause factors, measurable indicators, and early diagnosis. Comput Biol Med. 2018;102:234-41.
7. Evans AH, Okai D, Weintraub D, Lim SY, O'Sullivan SS, Voon V, et al. Scales to assess impulsive and compulsive behaviors in Parkinson's disease: critique and recommendations. Mov Disord. 219;34:791-8.
8. Vargas AP, Cardoso FE. Impulse control and related disorders in Parkinson's disease. Arq Neuropsiquiatr. 2018;76:399-410.
9. Uribe GJ, Pacheco OB. Trastorno de control de impulsos (TCI) en enfermedad de Parkinson. Acta Neurol Colomb. 2019;35:28-32.
10. De la Hoz EL. Trastorno de Control de Impulsos, una Comorbilidad Poco Estudiada en la Enfermedad de Parkinson; 2023. Available from: https://hdl.handle.net/2454/45649
11. Fernández-Prieto M, Lens M, López-Real A, Puy A, Dias-Silva JJ, Sobrido MJ. Alteraciones de la esfera emocional y el control de los impulsos en la enfermedad de Parkinson. Rev Neurol. 2010;50:S41-9.
12. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591-601.
13. Cervantes-Arriaga A, Rodríguez-Violante M, Villar-Velarde A, Corona T. Cálculo de unidades de equivalencia de levodopa en enfermedad de Parkinson. Arch Neurocien (Mex). 2009;14:116-9.
14. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A, et al. Expanded and independent validation of the Movement Disorder Society-unified Parkinson's disease rating scale (MDS-UPDRS). J Neurol. 2013;260:228-36.
15. Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. Questionnaire for impulsive-compulsive disorders in Parkinson's disease-rating scale. Mov Disord. 2012;27:242-7.
16. Ávila A, Cardona X, Bello J, Maho P, Sastre F, Martín-Baranera M. Trastornos del control de los impulsos y punding en la enfermedad de Parkinson: la necesidad de una entrevista estructurada. Neurología. 2011;26:166-72.
17. Parra-Medina LE, Góngora-Alfaro JL. Impulse control disorders: behavioral addictions in Parkinson's disease. Rev Neurobiol. 2020;11:061020.
18. Cervantes-Arriaga A, Rodríguez-Violante M, Yescas P, Alonso-Vilatela E. Fluctuaciones motoras en enfermedad de Parkinson. Rev Méd Inst Mex Seguro Soc. 2012;50:141-6.
19. Weintraub D, Mamikonyan E. Impulse control disorders in Parkinson's disease. Am J Psychiatry. 2019;176:5-11.
20. Zhang JF, Wang XX, Feng Y, Fekete R, Jankovic J, Wu YC. Impulse control disorders in Parkinson's disease: epidemiology, pathogenesis and therapeutic strategies. Front Psychiatry. 2021;12:635494.
21. Joutsa J, Martikainen K, Vahlberg T, Kaasinen V. Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease. Parkinsonism Relat Disord. 2012;18:1079-83.
22. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67:589-95.
23. Steeves TD, Miyasaki J, Zurowski M, Lang AE, Pellecchia G, Van Eimeren T, et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain. 2009;132:1376-85.
24. Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Paul J, et al. Dopamine agonist use is associated with impulse control disorders in Parkinson's disease. Arch Neurol. 2006;63:969-73.
25. Dongju S, Lacadie CM, Sinha R. Neural correlates and connectivity underlying stress-related impulse control difficulties in alcoholism. Alcohol Clin Exp Res. 2016;40:1884-94.
26. Theis H, Probst C, Fernagut PO, van Eimeren T. Unlucky punches: the vulnerability-stress model for the development of impulse control disorders in Parkinson's disease. NPJ Parkinsons Dis. 2021;7:112.
27. Rizo-Curiel G, Villaseñor-Cabrera T, Jarne-Esparcia A, Zuñiga-Ramírez C, Soto-Escageda A. Factores de riesgo para desarrollar Trastorno del control de los impulsos en Enfermedad de Parkinson. Arch Neurocien. 2018;10:9-14.
28. Erga AH, Alves G, Tysnes OB, Pedersen KF. Impulsive and compulsive behaviors in Parkinson's disease: impact on quality of and satisfaction with life, and caregiver burden. Parkinsonism Relat Disord. 2020;78:27-30.
29. Baumann-Vogel H, Valko PO, Eisele G, Baumann CR. Impulse control disorders in Parkinson's disease: don't set your mind at rest by self-assessments. Eur J Neurol. 2015;22:603-9.
30. Biundo R, Weis L, Abbruzzese G, Calandra-Buonaura G, Cortelli P, Jori MC, et al. Impulse control disorders in advanced Parkinson's disease with dyskinesia: the ALTHEA study. Mov Disord. 2017;32:1557-65.

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ORIGINAL ARTICLE

Neuropsychological characteristics of asymptomatic patients with HIV: cross-sectional study

Características neuropsicológicas de pacientes con VIH asintomáticos: estudio transversal

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Abstract

Background: *Human immunodeficiency virus (HIV) infects macrophages, microglia and astrocytes producing inflammation, damage and neuronal death, which can cause HIV-associated neurocognitive disorder.* **Method:** *A group of 30 HIV patients with adherence to antiretroviral therapy (ART) underwent a battery of tests to assess attention, memory, visuospatial skills, executive functions (working memory, processing speed, verbal fluency, planning and abstraction), mood (depressive and anxious symptomatology) and daily functioning.* **Results:** *30% of patients presented characteristics of asymptomatic neurocognitive impairment, and 10% presented minor neurocognitive disorder. In mood, 83.3% of the patients presented depres sive symptomatology and 66.6% presented anxious symptomatology. Negative and positive correlations were found between cognitive abilities and serological variables. Cognitive impairment with subtle failures derived from HIV infection in the central nervous system is present in patients despite adherence to ART. While viral load remains undetectable, mild cognitive impairment is possible. When there is a decrease in CD4 cells, impairment may also occur. The presence of depressive and anxious symptomatology is frequent in HIV, so a neuropsychological intervention focused on mood is important in these patients.* **Conclusions:** *We emphasize the need for comprehensive care in patients with HIV that favors adherence to ART, neuropsychological and mood assessment, and intervention.*

Keywords: *Asymptomatic HIV. HIV-associated neurocognitive disorder. Neuropsychological assessment.*

Resumen

Antecedentes: *El virus de la inmunodeficiencia humana (VIH) infecta macrófagos, microglías y astrocitos, produciendo inflamación, daño y muerte neuronal. Todo ello puede causar trastorno neurocognitivo asociado al VIH.* **Método:** *A un grupo de 30 pacientes con VIH, con adherencia al tratamiento antirretroviral (TARV), se le aplicó una batería de pruebas para evaluar la atención, la memoria, las habilidades visuoespaciales, las funciones ejecutivas (memoria de trabajo, velocidad de procesamiento, fluidez verbal, planeación y abstracción), el estado de ánimo (sintomatología depresiva y ansiosa) y la funcionalidad diaria.* **Resultados:** *El 30% de los pacientes presentó características de alteración neurocognitiva asintomática y el 10% presentó trastorno neurocognitivo menor. En cuanto al estado de ánimo, el 83.3% de los pacientes presentó sintomatología depresiva y el 66.6% sintomatología ansiosa. Se encontraron correlaciones negativas y positivas entre las*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000020

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):80-90
www.archivosdeneurociencias.mx

habilidades cognitivas y las variables serológicas. El deterioro cognitivo con fallas sutiles derivadas de la infección por VIH en el sistema nervioso central se presenta en los pacientes a pesar de tener adherencia al TARV. Si bien la carga viral se mantiene indetectable, es posible que haya deterioro cognitivo leve. Cuando hay disminución en las células CD4, también puede haber deterioro. La presencia de sintomatología depresiva y ansiosa es frecuente en los pacientes con VIH, y por ello es importante una intervención neuropsicológica enfocada en el estado de ánimo en estos pacientes. **Conclusión:** *Se enfatiza la necesidad de una atención integral en los pacientes con VIH que favorezca la adherencia al TARV, la evaluación y la intervención neuropsicológica y del estado de ánimo.*

Palabras clave: *VIH asintomático. Trastorno neurocognitivo asociado al VIH. Evaluación neuropsicológica.*

Introduction

From the early stages of the infectious process in the body, the human immunodeficiency virus (HIV) can cause infection of macrophages, microglia, and astrocytes, leading to neuronal damage[1]. The infection of macrophages triggers the release of cytokines, inducing proinflammation and the release of viral proteins gp120 and gp41, which can lead to irreversible neuronal damage and metabolic disruption, potentially resulting in cognitive decline[1,2]. Structural and functional neuroimaging modalities, such as magnetic resonance imaging, have reported 7.3% atrophy in the frontal lobe, 8% in the parietal lobe, and 0.15% in the temporal lobe; abnormal activation in the frontostriatal circuit, decreased cerebral blood volume in the frontal and parietal lobes, and glutamatergic reduction in the gray matter[3]; as well as cortical thinning of around 15% in parietal, frontal, and temporal regions, and in the orbitofrontal, cingulate, motor, and sensory cortex after 13 years of infection vs healthy controls[3].

Although there is still no cure, antiretroviral therapy (ART) allows control of HIV infection by reducing the viral load (VL)[4], and is, therefore, considered a chronic disease that remains asymptomatic when controlled. In the asymptomatic phase of HIV, there are no opportunistic infections that affect physical health[5]. However, it has been reported that even with ART, the virus remains in the body, showing cognitive impairments[6], highlighting the importance of working with this population to timely identify potential cognitive impairments and intervene by stimulating cognitive processes to favor an optimal state that benefits the quality of life of people living with HIV.

Former studies have reported that it is possible to identify attention deficits[7], visual and verbal memory failures, learning deficiencies, and difficulties in visuospatial abilities and executive functions in patients with HIV, including working memory, processing speed, and verbal fluency[8].

To assess HIV-associated cognitive decline, the Frascati criteria[9] are currently used, employing the generic term "HIV-associated neurocognitive disorder" (HAND), including a spectrum of 3 levels of cognitive impairment: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and major neurocognitive disorder (HAD, HIV associated dementia). Prevalence has been reported at 33% for ANI, 12% for MND, and 2% for HAD[11,12].

ANI and MND are characterized by subtle changes in working memory, processing speed, and verbal fluency, as well as slow learning or verbal memory failures[8]. Specifically, the Frascati criteria[9] state that ANI is identified in the presence of performance of, at least, 1 standard deviation (SD) below the mean in 2 or more cognitive domains without functional impairment. On the other hand, MND is established in the presence of changes in 2 or more cognitive domains, with performance or, at least, 1 SD below the mean, and mild-to-moderate interference in activities of daily living[8]. HAD usually develops in advanced stages of the infection and presents as subcortical dementia, with cognitive function, at least, 2 SD below the mean in 2 or more cognitive-motor domains and significant interference in daily functioning[9]; in HAD, attentional, concentration, memory, and processing speed failures are observed[8,13].

Several studies have identified neuropsychological characteristics in patients with HIV using the Frascati criteria[9,14-16], but evaluations have not included all elements to be considered in the criteria, such as cognitive domains, daily functionality, and mood state. The AIDS Study Group (GeSIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology[8] establishes that cognitive evaluations in patients with HIV should include 2 standardized tests per cognitive domain, mood and functionality scales. In general, studies focus on identifying the prevalence of HAND by evaluating only cognitive domains[15,16]; some evaluate functionality[14], and few assess mood state[14]. It is necessary to evaluate the mood state because anxious[17] and depressive[18,19] symptoms are frequent in this population and may influence self-care and quality of life[6].

It is also important to determine whether serological variables (VL, CD4 T lymphocytes, ART, and progression time) are associated with neuropsychological variables (cognitive, mood, and functional) to identify their relationship in the progression of the cognitive state, allowing a better understanding of the effects of HIV on cognition.

Obtaining the complete clinical picture and identifying whether serological variables are related to cognitive state, mood state, and functionality will allow the development of interventions tailored to the needs of patients with HIV. For these reasons, the present study addressed the 3 mentioned processes to obtain a complete neuropsychological profile in patients with HIV (cognitive, mood, and functional) as a basis for the development of future interventions.

The objective of the present study was to describe the neuropsychological characteristics of asymptomatic HIV patients, considering cognitive processes, mood state, and daily functionality, to identify any potential cognitive decline, as well as to explore whether these processes correlate with serological variables.

Method

Design

We conducted a cross-sectional descriptive observational study from May 2022 through May 2023[20]. This research design is appropriate to cover the objective because it allows the evaluation of variables of interest (cognitive domains, mood state, functionality, and serological variables) over a set period and to identify possible associations in a specific population based on inclusion and exclusion criteria to determine the frequency of HAND and assess potential impacts on mood and functionality.

Participants

The study included a total of 30 asymptomatic HIV-infected patients who were users of a specialized clinic in Mexico City, Mexico. The selection criteria were men and women aged 20 to 45 years, with, at least, a primary education level, and adherence to ART for, at least, 3 months. Exclusion criteria included neurological or psychiatric history (except for anxiety and depression), traumatic brain injuries, cerebrovascular diseases, and opportunistic infections. The sample consisted of 22 men and 8 women, with a mean age of 32.5 years (SD, 7.28). The serological characteristics are shown in table 1, showing that the patients had an undetectable VL and an adequate CD4 cell count, in addition to ART adherence. The progression time, ART duration, and ART regimen were reported directly by the patients, while VL and CD4 cell counts were obtained from laboratory tests performed every 3 months at the same specialized clinic (Table 1).

Instruments

The selection of neuropsychological instruments was based on GeSIDA's[8] recommendations for neuropsychological evaluation. The cognitive abilities evaluated included attention using the direct digits test from the Barcelona Test (PIEN)[21] and interference from the Stroop Test[22]; memory with the immediate and delayed text recall and word learning from PIEN[21]; visuospatial abilities with the Rey figure from NEUROPSI AyM[23]; and executive functions (working memory, processing speed, verbal fluency, planning, and abstraction) with the digit and letter test from the Wechsler Adult Intelligence Scale[24] (WAIS IV), word reading from the Stroop Test[22], categorical recall from PIEN[21], the zoo test from the Behavioral Assessment of the Dysexecutive Syndrome[24] (BADS), and similarities from WAIS IV[24]. Validity and normative data by cognitive domain are presented in table 2. Mood state was also evaluated, considering depressive and anxious symptoms, with the Patient Health Questionnaire[26] (PHQ-9) and the Generalized Anxiety Disorder Scale[27] (GAD-7); and daily functionality with the Activities of Daily Living Questionnaire[28] (T-ADLQ) (Table 2).

Procedure

A civil association working within the specialized clinic provided the phone numbers of the users who attended their services so that they could be contacted. Those who agreed to participate were informed of the study objective and signed an informed consent form. Subsequently, an expert neuropsychologist who knew how to administer, score, and interpret the mentioned instruments evaluated all participants with the neuropsychological battery in person. To control for potential biases, all participants were administered the same battery in a 2-hour session, in the same order, and in the same space with appropriate conditions at the specialized clinic. Evaluated participants received a free report of their neuropsychological evaluation. The collected information was entered into a database, maintaining the anonymity of the participants, for statistical

Table 1. Serological characteristics of patients

Characteristic	Mean	SD	Minimum	Maximum
Duration of illness, years	4.00	5.05	1	18
Duration on ART, years	3.50	4.52	1	18
Viral load	40.00	7.39	35	80
CD4 count	431.50	454.27	200	2467
ART regimen	Biktarvy®[a]	Atripla®[b]	Other[c]	
Patients	25	2	3	

SD: standard deviation; ART: antiretroviral therapy.
[a]Bictegravir, emtricitabine, and tenofovir.
[b]Emtricitabine, tenofovir, and efavirenz.
[c]Tenofovir, emtricitabine, dolutegravir, darunavir, and ritonavir.

analysis. The information is stored by the principal investigator in both physical (records in print) and digital formats.

Statistical analysis

The analyses were conducted using the SPSS statistical package. Descriptive statistics were used to obtain means, SDs, and ranges, and z-scores were used to analyze individual cases. Spearman's rho with $p \leq 0.05$ was used for correlation with serological variables, and the Benjamini-Hochberg procedure was used as an adjustment method. Spearman's rho was used because the PHQ-9 and GAD-7 instruments are Likert-type scales, i.e., with ordinal measurement variables. The variables considered for correlation were serological characteristics, cognitive abilities, mood state, and daily functionality.

Ethical aspects

Patients voluntarily agreed to be evaluated and signed an informed consent form. The study was approved by Facultad de Estudios Superiores Iztacala, UNAM Ethics Committee, number CE/FESI/082021/1418.

Results

In table 3, the group results obtained from the neuropsychological evaluation are shown. To standardize the scores of the instruments used, they were transformed into z-scores for attention, visual memory, verbal memory, visuospatial skills, and executive functions (working memory, processing speed, verbal fluency, planning, and abstraction). The highest score can be identified in BADS[25] Zoo (planning) and the lowest score in PIEN[21] text encoding (verbal memory).

In daily functioning, patients generally did not report impairment in their daily activities ($\bar{X} = 9.09$). It was also observed that, on average, they exhibited mild anxiety symptoms ($\bar{X} = 9.00$) and moderate depressive symptoms ($\bar{X} = 13.00$).

As seen in table 4, it was found that with longer disease duration and longer time on ART, participants showed lower cognitive performance, and with a higher CD4 count, they showed better cognitive performance. No correlations were observed with daily functioning or mood.

In a qualitative case analysis, 40% of the patients showed significant deficiencies in cognitive abilities. Table 5 shows that after transforming the neuropsychological battery scores to z-scores, 30% of participants met criteria for ANI and 10% met criteria for MND. A total of 23.3% scored –1 SD and 16.6% –2 SD below the mean in 2 or more cognitive regions. Regarding daily functioning, 16.6% of the participants showed mild impairment. These low scores were observed in attention, memory, visuospatial skills, and executive functions. Figure 1 illustrates the percentages of cognitive impairment by domain, based on z-scores. Regarding mood, 83.3% of the patients showed depressive symptoms, with 23.3% being mild, 13.3% moderate, 20% moderate to severe, and 26.6% severe; and 66.6% of the patients showed anxiety symptoms, with 20% mild, 16.6% moderate, and 30% severe.

Discussion

The aim of the study was to describe the cognitive, mood, and functional characteristics of asymptomatic

Table 2. Validity and normative data of the instruments used

Instrument	Cognitive domain	Validity	Reliability	Scoring	Normative data
PIEN[21]	Attention, memory, verbal fluency	Factorial structure explaining 41.9% of accumulated variance	Intraclass index of 0.99	Percentile	Age profiles from 20 years onwards and education from < 5 to > 8 years
Stroop test[22]	Attention, processing speed	Multivariate regression explaining 42% of accumulated variance	Test-retest of 0.884	Percentile	Age profiles from 18 years onwards and education up to 12 years and > 12 years
NEUROPSI AyM[23]	Visuospatial skills	-	0.828 for copying and 0.783 for delayed memory	Scaled score	Age profiles from 6 to 85 years and education from 0 to 22 years
WAIS IV[24]	Working memory and abstraction	Confirmatory factor analysis from–0.01 to 0.92	Between 0.75 and 0.91	Scaled score	Age profiles from 16 to 90 years
BADS[25]	Planning	Confirmatory factor analysis from 0.24 to 0.66	Cronbach's alpha of 0.87	"Profile" score from 1 to 4, with scores of 3 and 4 indicating normality	Age profiles from 16 to 87 years
PHQ-9[26]	Depressive symptoms	Factor analysis from 0.58 to 0.73	Cronbach's alpha of 0.89	Likert scale with cut-off scores for minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe depression (20-27)	Adolescents and adults
GAD-7[27]	Anxiety symptoms	Factorial structure explaining 63% of accumulated variance and factor analysis from 0.69 to 0.81	Cronbach's alpha of 0.93	Likert scale with cut-off scores for no anxiety (0-4), mild (5-9), moderate (10-14), and severe (15-21)	Adolescents and adults
T-ADLQ[28]	Daily living activities	Convergent validity ($r = 0.77$; $p < 0.001$)	Cronbach's alpha of 0.861	Summative scale where scores above 30% may indicate mild impairment	Adults

BADS: Behavioral Assessment of the Dysexecutive Syndrome; GAD-7: Generalized Anxiety Disorder Scale; NEUROPSI AyM: NEUROPSI Attention and Memory; PHQ-9: Patient Health Questionnaire; PIEN: Barcelona Test; T-ADLQ: Technology-Activity of Daily Living Questionnaire; WAIS IV: Wechsler Adult Intelligence Scale IV. Scaled scores have a mean of 10 and a standard deviation (SD) of 3, and percentile scores have a mean of 50 and an SD of 10.

HIV patients and their correlation with serological variables. Similar to what has been reported in the literature[10,13], low scores were observed in attention, memory, executive functions, and visuospatial abilities. Analyzing these data according to the Frascati criteria[9], the results suggest the presence of ANI in 30% of the participants evaluated and the presence of MND in 10%. These figures are similar to the higher rates described in some studies, which report the presence of ANI in 10.5% up to 47.5%[7,14,16,29,30] and MND in 5% up to 10.5%[13,15]; however, although these figures have been determined using the Frascati criteria[9], only the cognitive aspect was evaluated. This high rate of patients with cognitive impairment could imply that, although people with HIV may function well in their daily lives, subtle impairments need to be detected in a comprehensive neuropsychological evaluation[6] and cognitive stimulation programs should be developed to strengthen these domains,

Table 3. Performance results of patients on the neuropsychological assessment battery

Cognitive domain		Subtest	Mean	SD	Minimum	Maximum
Attention		PIEN[21] direct digits	5.55	1.00	–1.30	1.42
		Stroop[22] interference	6.66	0.99	–1.37	1.95
Memory	Visual	Rey Figure[23] (recall)	–1.00	1.00	–2.16	1.40
	Verbal	IT coding	–3.33	1.00	–1.37	2.13
		IT recall		–6.66	0.99	–1.20
		Word learning		1.66	0.99	–1.51
Visuospatial skills		Rey Figure[23] (copy)	6.66	1.00	–2.69	0.91
Executive functions	Working memory	WAIS IV[24] digits and letters	1.66	0.99	–1.94	2.54
	Processing speed	Stroop[22] word	3.33	1.00	–1.62	1.68
	Verbal fluency	PIEN[21] phonological recall	6.66	1.00	–1.28	1.96
	Planning	BADS[25] Zoo	9.25	0.99	–1.96	1.31
	Abstraction	WAIS IV[24] similarities	1.00	1.00	–1.87	2.02
Depression		PHQ-9[26]	13.00	7.76	0	24
Anxiety		GAD-7[27]	9.00	6.61	0	21
Daily dunctioning		T-ADLQ[28]	9.09	12.81	0	46.46

BADS: Behavioral Assessment of the Dysexecutive Syndrome; SD: standard deviation; GAD-7: Generalized Anxiety Disorder Scale; PHQ-9: Patient Health Questionnaire; PIEN: Barcelona Test; T-ADLQ: Technology-Activity of Daily Living Questionnaire; IT: immediate text; WAIS IV: Wechsler Adult Intelligence Scale IV.

Table 4. Correlations between cognitive abilities and serological variables

			Progression	Time on ART	VL	CD4	ART scheme	Benjamini-Hochberg correlation
Executive functions	Processing speed (Stroop[22] word)	Correlation coefficient	0.36	0.31	0.14	0.27	0.21	0.11
		Sig. (bilateral)	0.04	0.09	0.45	0.14	0.24	
	Zoo test (BADS[25])	Correlation coefficient	–0.40a	–0.37	–0.39	–0.12	–0.40	0.04[a]
		Sig. (bilateral)	0.02	0.04	0.03	0.52	0.02	
	Phonological recall (PIEN[21])	Correlation coefficient	–0.28	–0.39a	–0.20	–0.07	–0.27	0.04[a]
		Sig. (bilateral)	0.12	0.04	0.26	0.70	0.14	
	Digits and letters (WAIS IV[24])	Correlation coefficient	0.13	–0.02	0.38	0.41a	0.19	0.02[a]
		Sig. (bilateral)	0.49	0.88	0.03	0.02	0.30	
Memory	IT encoding (PIEN[21])	Correlation coefficient	0.05	0.02	0.38	0.44a	0.00	0.01[a]
		Sig. (bilateral)	0.78	0.89	0.03	0.01	0.97	

BADS: Behavioral Assessment of the Dysexecutive Syndrome; VL: viral load; PIEN: Barcelona Test; ART: antiretroviral treatment; IT: immediate text; WAIS IV: Wechsler Adult Intelligence Scale IV.
[a]Significant corrected correlations.

prevent progression to HAD, and provide comprehensive care for patients, including medical, emotional, and neuropsychological attention.

Subtle changes may occur due to HIV infection in the central nervous system, which generates a particular pathophysiology with infection of lymphocytes, monocytes,

Table 5. Performance results by patient on the neuropsychological assessment battery, shown in z-scores

Participant	Visual attention		Memory				Visuospatial skills	Executive functions					Mood		T-ADLQ[28] Daily functionality
			Verbal (PIEN[21])												
	PIEN[21] Direct digits	Stroop[22] interference	Rey Figure recall	IT encoding	TI recall	Word learning	Rey Figure (copy)	WAIS IV[24] Digits and letters	Stroop[22] words	PIEN[21] phonological recall	BADS Zoo Test[25]	WAIS IV[24] similarities	PHQ-9[26] depression	GAD-7[27] anxiety	
1	0.41	2.05	0.70	−0.22	0.02	0.65	0.77	−0.24	0.86	0.11	0.95	0.32	16	16	10.10%
2*	−0.54	0.19	0.19	−0.22	0.19	−0.27	**−3.28**	0.14	−0.22	−0.06	−0.31	**−1.28**	0	0	2.02%
3*	**−1.50**	−0.56	−0.12	**−2.62**	**−2.28**	**−1.55**	0.77	**−1.40**	−0.61	**−1.77**	−0.31	**−1.97**	8	2	0%
4*	−0.54	−0.09	−0.32	−0.38	**−1.62**	**−1.44**	0.21	**−1.02**	−0.15	**−1.43**	0.11	**−1.74**	12	10	0%
5	0.41	−0.32	0.70	0.89	1.01	1.00	−0.34	1.30	1.40	0.28	−0.73	−0.36	11	6	19.20%
6	−0.54	1.01	0.08	**−1.50**	0.35	0.30	0.21	−0.63	−0.46	0.36	0.95	−0.36	2	2	8%
7	0.41	−0.30	0.70	0.41	−0.13	0.19	0.49	−0.24	−0.38	−0.66	0.53	−0.13	5	0	18.18%
8	−0.54	−0.28	0.91	1.53	1.84	0.54	0.77	0.14	0.86	0.02	−0.73	0.32	17	17	6.06%
9	1.37	**−1.72**	0.91	0.09	−0.13	1.00	0.77	0.91	0.86	0.54	−0.31	1.94	6	2	5.05%
10*	−0.54	**−1.10**	−0.74	−0.06	−0.46	0.54	0.49	**−1.02**	−0.30	−0.31	0.11	1.02	2	2	0%
11	0.41	**−1.13**	1.32	1.53	1.01	0.89	−0.06	−0.24	−0.07	1.48	0.95	0.09	9	7	9.09%
12	0.41	1.26	0.29	1.37	0.68	1.12	−0.34	2.08	0.86	−0.74	**−2.85**	0.32	2	4	11%
13*	0.41	1.74	1.12	**−1.66**	**−1.29**	1.00	0.77	0.91	−0.54	0.28	0.95	**−1.05**	17	17	8.08%
14	**−1.50**	0.49	−0.32	0.09	1.51	−0.04	−0.34	0.14	0.86	−0.06	−0.31	1.71	21	16	25.25%
15	−0.54	−0.32	−0.12	−0.06	0.19	−0.85	**−1.46**	0.91	0.86	3.97	0.95	1.25	17	10	9.09%
16*	0.41	**−1.49**	0.91	0.89	0.68	**−1.44**	0.21	0.14	0.86	0.19	0.95	0.32	6	9	2.02%
17	1.37	−0.31	**−2.08**	**−1.18**	0.02	0.42	0.77	0.14	0.08	−0.06	0.53	0.32	24	17	23.23%
18**	**−1.50**	0.10	0.29	−0.54	−0.13	−0.39	0.77	−0.24	**−1.00**	**−1.17**	0.95	0.79	22	15	40.40%
19**	**−2.46**	0.57	**−1.67**	−0.38	**−2.12**	**−2.02**	**−2.16**	**−2.18**	**−2.95**	−0.31	0.11	−0.82	24	19	34.34%

(Continues)

Table 5. Performance results by patient on the neuropsychological assessment battery, shown in z-scores *(continued)*

Participant	Visual attention		Memory				Visuospatial skills	Executive functions					Mood		T-ADLQ[28] Daily functionality
			Verbal (PIEN[21])												
	PIEN[21] Direct digits	Stroop[22] interference	Rey Figure recall	IT encoding	TI recall	Word learning	Rey Figure (copy)	WAIS IV[24] Digits and letters	Stroop[22] words	PIEN[21] phonological recall	BADS Zoo Test[25]	WAIS IV[24] similarities	PHQ-9[26] depression	GAD-7[27] anxiety	
20*	1.37	**–1.10**	**–1.77**	–0.54	–0.46	**–2.25**	**–1.74**	**–1.02**	–0.61	–0.06	**–2.42**	**–1.05**	11	5	11.11%
21**	–0.54	**–1.26**	0.70	**–1.18**	–0.13	0.19	0.49	0.14	–0.38	0.28	0.95	0.09	14	9	32.30%
22	1.37	0.89	0.91	0.57	0.85	0.42	0.77	–0.24	0.78	–0.48	0.53	–0.13	24	19	17.17%
23	1.37	–0.19	0.50	0.73	1.67	1.12	0.77	2.46	0.86	0.02	**–1.15**	0.32	21	8	30.30%
24	0.41	–0.40	0.29	–0.22	–0.13	–0.27	–0.06	0.14	**–1.71**	–0.74	**–1.58**	**–1.05**	21	21	46.46%
25	–0.54	0.89	0.50	–0.38	–0.79	0.65	0.77	0.52	0.70	–0.06	–0.31	0.79	5	4	6.06%
26	0.41	1.14	0.29	1.21	–0.30	0.89	–0.34	–0.24	0.47	0.88	–0.31	0.32	18	11	7.07%
27*	–0.54	–0.25	**–1.67**	–0.06	0.35	0.07	–0.62	–0.27	**–1.71**	–0.06	0.53	–0.82	19	10	18.18%
28*	0.41	1.43	–2.19	1.05	0.35	–0.74	–0.06	**–1.40**	0.86	–0.06	0.11	**–1.28**	16	14	4.04%
29	1.37	0.38	0.50	1.05	0.19	1.23	0.21	0.91	0.86	0.45	0.95	1.48	7	2	2.02%
30	–0.54	**–1.30**	–0.84	–0.22	–0.96	–0.97	0.77	–0.63	–0.93	–0.83	0.11	0.56	1	0	0%

BADS: Behavioral Assessment of the Dysexecutive Syndrome; GAD-7: Generalized Anxiety Disorder Scale; NEUROPSI AyM: NEUROPSI Attention and Memory; PHQ-9: Patient Health Questionnaire; PIEN: Barcelona Test; T-ADLQ: Questionnaire on Activities of Daily Living and Technology; IT: immediate text; WAIS IV: Wechsler Adult Intelligence Scale IV.
Highlighted results indicate scores < 1 or 2 standard deviations (SD). Participants marked with an asterisk exhibit characteristic of ANI if they have 2 or more scores < 1 or 2 SD. Participants marked with 2 asterisks exhibit characteristics of MND if they have 2 or more scores < 1 or 2 SD. Cut-off points for identifying depressive symptoms (PHQ-9) are: 0-4 minimal depression, 5-9 mild, 10-14 moderate, 15-19 moderately severe, and 20-27 severe. Cut-off points for identifying anxious symptoms (GAD-7) are: 0-4 no anxiety, 5-9 mild anxiety, 10-14 moderate anxiety, and 15-21 severe anxiety.

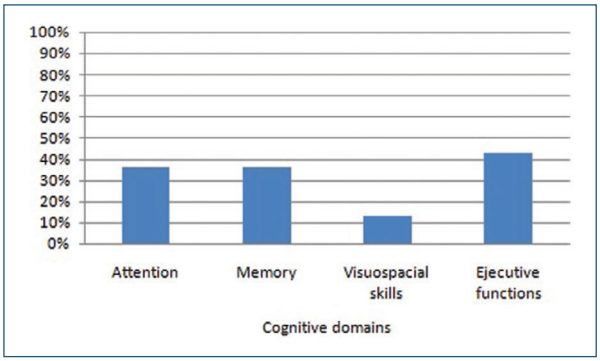

Figure 1. Percentage of patients who showed cognitive impairment by domain.

perivascular macrophages, microglia, and astrocytes, which in turn triggers the release of cytokines and viral proteins gp120 and gp41 that cause neuronal damage and metabolic disruption[1]. Although major neurocognitive disorder does not always develop due to ART, it has been shown that, despite this, the presence of the virus in the central nervous system remains, specifically in the cerebrospinal fluid[31], which could partially explain the cognitive impairment reported in up to 50% of cases[6]. In the serological variables of the patients, a mean progression time of 4 years, a mean of 3.5 years of ART adherence, a VL of 40.00 copies, and a mean CD4 count of 431.50 were observed, indicating an asymptomatic serological state with undetectable VL; however, it has been reported that despite this, some cognitive impairment may still be identified[6]. It has also been reported that if the HIV infection is in an asymptomatic state, only ANI or even a relatively adequate cognitive state may be found, yet if the CD4 count drops (< 200), cognitive impairment may occur, or if it is already present, it may progress to a severe form[6,32]. Therefore, it is suggested to start ART as early as possible to strengthen the immune system and also provide neuropsychological follow-up[6,32].

An important finding of the study was the presence of anxiety and depressive symptoms in 66.6 and 83.3% of the patients, respectively. In the literature, it has been identified that in people with HIV, the incidence of depression is twice as high as in the general population and can be observed in up to 30% of cases[18,19]. It has been suggested that untreated depressive states may increase substance abuse and risky behaviors, reduce ART adherence, and decrease the quality of life of people with HIV[19]. Anxiety symptoms can occur due to the implications of living with a chronic illness such as HIV infection[17]. The effect of social stigma[17] associated with having HIV often causes family and social networks to fade away, leading to feelings of fear, shame, stress, sadness, or frustration in patients. Furthermore, facing life changes, uncertainty about the future, and possibly death can cause feelings of anxiety[33]. Therefore, the psychological state of people with HIV can affect their quality of life, an impact that may even be greater vs the physical state on their quality of life[6].

The limitations of the study include a small sample size[34] and the lack of a comparative group[35]. These limitations may hinder the generalization of the results, so they should be interpreted with caution[34]. However, the findings allow us to visualize the neuropsychological needs of asymptomatic HIV patients and highlight the elements that should be included in interventions. Therefore, the next step for future research is to evaluate larger samples and make comparisons with healthy individuals to have greater experimental control and a reference parameter for the cognitive, functional, and mood profile of patients, and the expected outcomes after conducting a neuropsychological intervention. Regarding the study design, it was not possible to establish causal relationships in the analyses[20], so future studies should consider an explanatory design[20] that allows for a deeper understanding of the relationship between serological and neuropsychological variables to better understand the effects of HIV on cognition.

Conclusions

It was identified that 30% of asymptomatic HIV participants show ANI and 10%, MND. Regarding mood state, 83.3% of the patients showed depressive symptoms and 66.6% anxiety symptoms. Additionally, a correlation was found between cognitive functioning and the serological characteristics of the patients. The importance of providing comprehensive care to this population is emphasized, starting ART as early as possible and emphasizing both neuropsychological evaluation and intervention[6], which should include work on mood state and cognitive stimulation exercises focused on attention, memory, and executive functioning. Furthermore, the intervention should have an ecological component to make it possible to generalize the strategies used in stimulation to everyday life.

Finally, the discrepancy identified in mood state is emphasized. Some former studies reported depressive symptoms in up to 30% of cases[18,19], while in the present study, depressive symptoms were identified in

83.3%. Regarding the prevalence of HAND, our results (ANI in 30% and MND in 10%) are similar to those reported by former studies (ANI in 10.5% up to 47.5%[7,14,16,29,30] and MND in 5% up to 10.5%[13,15]).

Acknowledgments

To National Council of Science and Technology (CONACYT) for the scholarship provided to N. Cortés Corona, with CVU number 854886, for pursuing doctoral studies in Psychology at the Universidad Nacional Autónoma de México. Also to Casa de la Sal A.C. and the Condesa Iztapalapa Specialized Clinic.

Authors' contributions

N. Cortés-Corona made a substantial contribution to the conception and design of the work, the acquisition, analysis, and interpretation of data, and the drafting of the manuscript. M.G. Yáñez-Téllez supervised the method, data collection and analysis, and advised the lead author in the development of this research and the drafting of the manuscript with a critical review of the intellectual content. B. Prieto-Corona advised the lead author in the development of this research and the drafting of the manuscript with a critical review of the intellectual content. E. Landa-Ramírez contributed to the methodological aspects of the study, writing, and critical review of the intellectual content.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed their workplace protocols on the publication of patient data.

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

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

References

1. Rojas-Celis V, Valiente-Echeverría F, Soto-Rifo R, Toro-Ascuy D. New challenges of HIV-1 infection: how HIV-1 attacks and resides in the central nervous system. Cell. 2019;8:1245.
2. Arentoft A, Troxell K, Alvarez K, Aghvinian M, Rivera Mindt M, Cherner M, et al. HIV antiretroviral medication neuropenetrance and neurocognitive outcomes in HIV+ adults: a review of the literature examining the central nervous system penetration effectiveness score. Viruses. 2022;14:1151.
3. Chang L, Shukla DK. Imaging studies of the HIV-infected brain. Handb Clin Neurol. 2018;152:229-64.
4. Corley MJ, Sacdalan C, Pang APS, Chomchey N, Ratnaratorn N, Valcour V, et al.; SEARCH010/RV254 and SEARCH013/RV304 study groups. Abrupt and altered cell-type specific DNA methylation profiles in blood during acute HIV infection persists despite prompt initiation of ART. PloS Pathog. 2021;17:e1009785.
5. Parekh BS, Ou CY, Fonjungo PN, Kalou MB, Rottinghaus E, Puren A, et al. Diagnosis of human immunodeficiency virus infection. Clin Microbiol Rev. 2018;32:e00064-18.
6. Underwood J, Winston A. Guidelines for evaluation and management of cognitive disorders in HIV-positive individuals. Curr HIV/AIDS Rep. 2016;13:235-40.
7. Zaegel-Faucher O, Laroche H, Tixier M, Morisseau V, Obry-Roguet V, Poizot-Martin I. Is the use of the QPC cognitive complaints questionnaire relevant for the screening strategy of HIV-associated neurocognitive disorders? AIDS Care. 2021;33:389-97.
8. Grupo de expertos del Grupo de Estudio de Sida (GeSIDA). Documento de consenso sobre el manejo clínico de los trastornos neurocognitivos asociados a la infección por el virus de la inmunodeficiencia humana. Enferm Infecc Microbiol Clin. 2014;32:37-47.
9. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69:1789-99.
10. Kimani RW. Assessment and diagnosis of HIV-associated dementia. JNP. 2018;14:190-5.
11. Vázquez E, Rodríguez M. Influencia de factores no relacionados con la infección en el rendimiento neuropsicológico de seropositivos al VIH. Rev Neurol. 2002;35:474-80.
12. Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bently H. The impact of HIV-associated neuropsychological impairment on everyday functioning. J Int Neuropsychol Soc. 2004;10:317-31.
13. Cornea A, Lata I, Simu M, Rosca EC. Assessment and diagnosis of HIV-associated dementia. Viruses. 2023;15:378.
14. Agarwal R, Aujla RS, Gupta A, Kumar M. Determining the neurocognitive status and the functional ability of patients to screen for HIV-associated neurocognitive disorder (HAND). Dement Neurocogn Disord. 2020; 19:19-27.
15. Forno G, Henríquez F, Ceballos ME, González M, Schröder J, Toro P. Neurological soft signs (NSS) and cognitive deficits in HIV associated neurocognitive disorder. Neuropsychologia. 2020;146:107545.
16. Nakao A, Yamanouchi J, Takenaka K, Takada K. The Iowa Gambling Task on HIV-infected subjects. J Infect Chemother. 2020;26:240-4.
17. Yousuf A, Musa R, Isa MLM, Arifin SRM. Anxiety and depression among women living with HIV: prevalence and correlations. Clin Pract Epidemiol Ment Health. 2020;16:59-66.
18. Liu X, Wang H, Zhu Z, Zhang L, Cao J, Zhang L, et al. Exploring bridge symptoms in HIV-positive people with comorbid depressive and anxiety disorders. BMC Psychiatry. 2022;22:448.
19. Camara A, Sow MS, Touré A, Sako FB, Camara I, Soumaoro K, et al. Anxiety and depression among HIV patients of the infectious disease department of Conakry University Hospital in 2018. Epidemiol Infect. 2020;148:e8.
20. Setia MS. Methodology Series Module 3: cross-sectional studies. Indian J Dermatol. 2016;61:261-4.
21. Peña J. Normalidad, semiología y patología neuropsicológicas. Programa Integrado de Exploración Neuropsicológica. Test Barcelona. Barcelona: Masson; 1991.

22. Golden CJ. STROOP Test de colores y palabras. Madrid: TEA; 2001.
23. Ostrosky F, Gómez ME, Matute E, Rosselli M, Ardila A, Pineda D. NEUROPSI Atención y Memoria. Ciudad de México: Manual Moderno; 1997.
24. Wechsler D. Escala de Inteligencia de Wechsler para Adultos (WAIS-IV). Ciudad de México: Manual Moderno; 2010.
25. Wilson BA, Alderman N, Burgess P, Emslie H, Evans J. Behavioural Assessment of the Dysexecutive Syndrome (BADS). London: Pearson; 1999.
26. Diez C, Rangil T, Sánchez L, Kroenke K, Spitzer RL. Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients. Psychosom Med. 2001; 63:679-86.
27. García J, Zamorano E, Ruiz MA, Pardo A, Pérez M, López V, et al. Cultural adaptation into Spanish of the generalized anxiety disorder-7 (GAD-7) scale as a screening tool. Health Qual Life Outcomes. 2010;8:8.
28. Muñoz C, López OL, Riveros R, Núñez J, Flores P, Slachevsky A. The technology - activities of daily living questionnaire: a version with a technology-related subscale. Dement Geriatr Cogn Disord. 2012; 33:361-71.
29. Costaggiu D, Pinna E, Serchisu L, Barcellona D, Piano P, Ortu F, et al. The repeatable battery for the assessment of neuropsychological status as a screening strategy for HIV-associated neurocognitive disorders. AIDS Care. 2021;33:357-63.
30. Métral M, Darling K, Locatelli I, Nadin I, Santos G, Brugger P, et al. The Neurocognitive Assessment in the Metabolic and Aging Cohort (NAMACO) study: baseline participant profile. HIV Med. 2019;21:30-42.
31. Farhadian SF, Lindenbaum O, Zhao J, Corley MJ, Im Y, Walsh H, et al. HIV viral transcription and immune perturbations in the CNS of people with HIV despite ART. JCI Insight. 2022;7:e160267.
32. Wang Y, Liu M, Lu Q, Farrell M, Lappin JM, Shi J, et al. Global prevalence and burden of HIV-associated neurocognitive disorder: a meta-analysis. Neurol. 2020;95:e2610-21.
33. Kartikeyan S, Bharmal RN, Tiwari RP, Bisen PS. HIV and AIDS: basic elements and priorities. Netherlands: Springer; 2007.
34. Hackshaw A. Small studies: strengths and limitations. Eur Respir J. 2008;32:1141-3.
35. Cucherat M, Laporte S, Delaitre O, Behier JM; Giens XXXV Round Table Clinical Research; d'Andon A, et al. From single-arm studies to externally controlled studies. Methodological considerations and guidelines. Therapie. 2020;75:21-7.

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RESEARCH PROTOCOL

Clinical tools accuracy for classification of primary progressive aphasia: a systematic review protocol

Precisión de las herramientas clínicas para clasificación de la afasia progresiva primaria: protocolo de revisión sistemática

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Abstract

Background: *Primary progressive aphasia (PPA) is a syndrome characterized by progressive decline in language function. There are three main PPA syndromes, each one features different language profiles and neuropathologic substrates. Although there are current clinical diagnostic criteria for PPA categorization, the utility of these requires evaluation(s) by specialized staff and the administration of extensive cognitive batteries. A diagnostic tool for PPA is not currently standardized, though some batteries have been developed and/or validated exclusively for PPA categorization.* **Objective:** *To describe which cognitive/aphasia diagnostic tool has the best accuracy for PPA diagnosis and categorization.* **Methods:** *MEDLINE (PubMed), EMBASE, and Web of Science databases will be searched using adequate search strategies. Studies including original data of possible, probable, and definite PPA cases according to current clinical diagnostic criteria for PPA will be included. Quality assessment will be performed according to the Quality Assessment of Diagnostic Accuracy Studies-2 guidelines. This systematic review protocol is reported as stated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2015 statement.* **Results:** *Findings of this protocol will be published in a peer-review journal.* **Conclusions:** *Clinical diagnostic tools may facilitate the diagnosis of PPA.*

Keywords: *Primary progressive aphasia. Diagnostic test. Diagnostic battery.*

Resumen

Antecedentes: *La afasia progresiva primaria (APP) es un síndrome caracterizado por el declive progresivo en la función del lenguaje. Hay tres síndromes principales de APP, cada uno con perfiles lingüísticos y sustratos neuropatológicos diferentes. Aunque existen criterios diagnósticos clínicos actuales para la categorización de la APP, su utilidad requiere evaluaciones por personal especializado y la administración de extensas baterías cognitivas. En la actualidad no existe una herramienta diagnóstica estandarizada para la APP, aunque se han desarrollado y validado algunas baterías exclusivamente para su categorización.* **Objetivo:** *Averiguar qué herramienta diagnóstica cognitiva/afásica tiene la mejor precisión para el diagnóstico y la categorización de la APP.* **Método:** *Se realizará una búsqueda en las bases de datos*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000022

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):91-95
www.archivosdeneurociencias.mx

MEDLINE (PubMed), EMBASE y Web of Science utilizando estrategias de búsqueda adecuadas. Se incluirán estudios que contengan datos originales de casos de APP posibles, probables y definitivos según los criterios diagnósticos clínicos actuales para la APP. La evaluación de la calidad se realizará de acuerdo con las directrices de Estudios de Precisión Diagnóstica-2 (QUADAS-2). Este protocolo de revisión sistemática se reporta según lo establecido en la declaración Protocolo de los Artículos de Informes Preferidos para Revisiones Sistemáticas y Meta-Análisis (PRISMA-P) de 2015. **Resultados:** *Los hallazgos de este protocolo serán publicados en una revista de revisión por pares.* **Conclusiones:** *Las baterías clínicas pueden ayudar a facilitar el diagnóstico de APP.*

Palabras clave: *Afasia progresiva primaria. Prueba diagnóstica. Batería diagnóstica.*

Introduction

Primary progressive aphasia (PPA) is a syndrome of neurodegenerative nature characterized by progressive decline of language function. There are three main PPA syndromes: (1) Semantic variant PPA (svPPA), non-fluent variant PPA (nfvPPA), and logopenic variant PPA (lvPPA)[1]. Each one is affected by different language profiles, brain volume loss patterns, and neuropathology[2]. The identification and classification of PPA in clinical settings are still challenging. Furthermore, around 30-40% of PPA syndromes are not classifiable in any of the three main different phenotypes, these are known as mixed PPA syndromes[3]. Accurate classification of these variants is important for prognosis, clinical care improvement, clinical research, and enrollment in clinical trials.

Diagnosis and clinical classification of PPA are typically implemented through the addition of features of clinical history, characteristics of language deficits (e.g., anomia, agrammatism, speech apraxia, etc), neurological and cognitive examination, and structural and functional brain imaging or other biomarkers[4,5]. This approach is ideal, however, is time consuming and requires a multidisciplinary method. Some aphasia batteries such as the Boston Diagnostic Aphasia Examination[6] and the Western Aphasia battery[7] have been applied for PPA classification/diagnosis. However, these instruments were not originally developed for PPA, require special training for application, and are time-consuming. In search for a standardized and brief assessment tool for PPA identification and classification, some clinical batteries have been developed and/or validated in the past few years[8]. Examples include an automatic calculator that was created using individual item analysis of Addenbrooke's Cognitive Examination III, demonstrating good sensitivity for the classification of PPA syndromes[9]. A new brief language battery developed for PPA classification called "Mini Linguistic State Examination"[10] demonstrated excellent accuracy for the classification of each of the main three PPA variants. Another recently created brief screening tool named Progressive Aphasia Rating Scale "PARIS" is useful to distinguish between AD and PPA and even between lvPPA and svPPA[11]. Moreover, the effectiveness of PPA categorization has been demonstrated through the validation of the Sydney Language Battery "SYDBAT"[12].

Rationale

The current classification of patients with PPA in a clinical scenario requires evaluation by professionals with diverse type of training (e.g., cognitive neurology, neuropsychiatry, neuropsychology, etc). Although a multidisciplinary approach is ideal, it is expensive, time-consuming, and it is not available in most health centers worldwide. A clinical battery for an accurate classification of PPA variants is necessary for a better characterization even in places with trained physicians where there is not enough time to perform an extensive evaluation or in sites without trained staff for a good screening. Despite several batteries have demonstrated their effectiveness identifying PPA variants, to date, there are no evidence synthesis reports comparing the classification/diagnosis accuracy between these batteries. We performed a search in the international prospective register of systematic reviews (PROSPERO) and the open science framework on June 28, 2023. We found one scoping review protocol similar than our proposal (https://osf.io/hw82g). However, the present protocol will be focused exclusively on the comparison of the accuracy of diagnostic tools with a systematic review/meta-analysis methodology.

Research question

The primary research question is: what is the accuracy of cognitive batteries to correctly identify and classify patients with PPA syndromes? The target population is patients with the diagnosis of any of the three PPA variants. The index test will be any cognitive or language

battery that has demonstrated usefulness in the classification/diagnosis of a PPA syndrome considering PPA current clinical diagnostic criteria[1]. A diagnosis of PPA according to current clinical criteria including a language battery, brain imaging, and follow-up establishing the diagnosis will be taken as the reference standard (Table 1).

Table 1. Research question according to PIRD framework

PIRD	In patients with PPA (P) what is the clinical/cognitive/aphasia battery with the best classification accuracy (I) considering current clinical diagnostic criteria the reference (R) for PPA diagnosis (D)

PIRD: population, index test, reference test, diagnosis of interest; PPA: primary progressive aphasia.

Objectives

Primary objective

- To compare the accuracy of cognitive/aphasia batteries for diagnosis of PPA (any variant) according to current clinical diagnostic criteria
- To compare the accuracy of cognitive/aphasia batteries for diagnosis and classification of PPA-specific variants
- To describe the accuracy of cognitive/aphasia batteries comparing specific PPA variants (e.g., svPPA versus nfvPPA, svPPA versus lvPPA, etc.)

Secondary objective

To describe the meantime of application of the different cognitive/aphasia batteries that are useful for classification/diagnosis of PPA.

Methods

Literature search

Search strategy will be performed including MEDLINE (PubMed), EMBASE, and Web of Science. We developed a search strategy using 2dsearch. The search algorithm is publicly available at https://app.2dsearch.com/query/649b3268c26f12b434eb0aac. In addition, we will perform a search in Google Scholar including the first 100 results using Publish or Perish software. Titles and abstracts will be screened for eligibility by two independent reviewers, duplicates will be removed using covidence, and discrepancies will be resolved by discussion. This protocol is reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[13] and complemented with PRISMA Protocols statement (PRISMA-P). Results will be exhibited in a PRISMA flow diagram.

Inclusion criteria

Full texts of any type of test accuracy study including gray literature published since 2011 (as specific PPA diagnostic criteria were published in this year) in English or Spanish. Articles written in other languages will be included only if an appropriate translation is available using DeepL or Google translate.

The following inclusion criteria will be applied: Studies with original data (e.g., case-control, cross-sectional, cohort designs, etc.) (1) describing patients with a PPA diagnosis established with the current clinical diagnostic criteria, including possible, probable, or definite cases[1]. (2) Details of cognitive batteries describing measures for classification/diagnosis of PPA variants (e.g., sensitivity, specificity, positive predictive values, receiver-operating characteristic [ROC] curves, etc.). (3) Data of imaging, neuropsychological examination, genetic testing, and other type of evidence supporting the diagnosis of PPA according to current clinical diagnostic criteria.

Initial stage will include title and abstract screening for potential eligibility. Subsequently, full-text articles will be evaluated to determine inclusion and exclusion criteria. Data extraction will be performed using data collection forms by two independent reviewers. This form will be pilot tested using the first 25 samples. Screening and data extraction will be performed using covidence.

Exclusion criteria

- Studies describing PPA cases in advanced stages of the disease (severe dementia) according to a standardized cognitive battery such as Dementia Rating Scale[14], Clinical Dementia Rating[15], Mini-Mental State Examination[16] or other.
- PPA cases with mixed phenotypes that are difficult to categorize in one of the three main PPA variants according to current clinical diagnostic criteria[1]
- Studies in other languages than English or Spanish that could not be appropriately translated.

Data extraction

Extracted data will include the following:

- Details of the study: title, year of publication, country of origin, name of the first author, diagnostic cut point of each tool, and source(s) of funding
- Demographic data of participants
- Average time of battery administration
- Details of study methodology registering procedures, materials, ethics procedures
- Number of participants and details of how PPA diagnosis was performed, including biomarkers if available for each included study
- Type of test/battery applied to diagnose and classify PPA syndromes.
- Data of raters (e.g., if they were full trained to perform a specific battery)
- Test accuracy features to classify or diagnose a PPA syndrome (e.g., specificity, sensitivity, positive predicate values, negative predictive values, ROC curves, etc.).

Quality assessment

The study design and methods of selected studies will be evaluated according to the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) guidelines[17]. The assessment of evidence quality in QUADAS-2 guidelines includes four domains. (1) Participant selection: we will consider studies evaluating patients with PPA with a standardized battery and current clinical diagnostic criteria. (2) The index test will be any standardized cognitive or language battery tested for PPA categorization. (3) The reference standard will be the current clinical PPA diagnostic criteria. (4) For the flow and timing of assessments, we will consider 90 min as it is an approximate average time for the application of standardized aphasia batteries. Two reviewers will assess the quality independently and discrepancies will be resolved by discussion. A third reviewer will be consulted if discrepancies remained.

Data analysis

The test accuracy of each index test will be displayed in 'paired' forest plots and summary receiver-operating characteristic (SROC) curves of sensitivity and specificity including confidence intervals and means for each selected primary study. We will compute forest plots and SROC using RevMan software (Cochrane collaboration 2020). Heterogeneity will be estimated by visual inspection of SROC curve and objectively with Fisher's exact test.

Where clinical and methodological characteristics of included studies are homogeneous a bivariate random effect model for sensitivity and specificity will be performed using SPSS V.27.0. A narrative summary will be considered if a meta-analysis is not suitable.

Ethics and dissemination

This systematic review will use publicly available data from studies that obtained ethical approval without directly involving human participants. Therefore, ethics approval is not required. This protocol is registered and publicly available at the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42023440682. Findings of this systematic review protocol will be disseminated through a publication in a peer-reviewed journal. Results will be helpful in terms of diagnosis and classification of PPA syndromes.

Authors' contributions

RRG provided original idea, protocol development, topic expertise, manuscript writing, and coordination of coauthors; JAMG provided original idea, protocol development, protocol methodology, manuscript revision, and topic expertise; SG contributed with original idea, topic expertise, and manuscript revision; ORR contributed with manuscript revision; RMR provided manuscript revision; EF contributed with protocol development, topic expertise, and manuscript revision; IPN contributed with protocol development, methodology expertise, and manuscript revision.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Conflicts of interest

Ivan Perez-Neri is the editor in chief and Ramiro Ruiz-Garcia is editor of "Archivos de Neurociencias" journal.

Ethical disclosures

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

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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

References

1. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456-77.
2. Mesulam MM, Coventry CA, Bigio EH, Sridhar J, Gill N, Fought AJ, et al. Neuropathological fingerprints of survival, atrophy and language in primary progressive aphasia. Brain. 2022;145:2133-48.
3. Mesulam MM, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. Brain. 2012;135:1537-53.
4. Henry ML, Grasso SM. Assessment of individuals with primary progressive aphasia. Semin Speech Lang. 2018;39:231-41.
5. Marshall CR, Hardy CJ, Volkmer A, Russell LL, Bond RL, Fletcher PD, et al. Primary progressive aphasia: a clinical approach. J Neurol. 2018;265:1474-90.
6. Goodglass: The Assessment of Aphasia and Related Disorders-Google Académico. Available from: https://scholar.google.com/scholar_lookup?-title=the+assessment+of+aphasia+and+related+disorders&author=h+-goodglass&author=e+kaplan&publication_year=1993&
7. Kertesz A. The western aphasia battery: a systematic review of research and clinical applications. Aphasiology. 2020;36:1-30.
8. Matias-Guiu JA, Grasso SM. Primary progressive aphasia: in search of brief cognitive assessments. Brain Commun. 2022;4:fcac227.
9. Foxe D, Hu A, Cheung SC, Ahmed RM, Cordato NJ, Devenney E, et al. Utility of the Addenbrooke's cognitive examination III online calculator to differentiate the primary progressive aphasia variants. Brain Commun. 2022;4:fcac161.
10. Patel N, Peterson KA, Ingram RU, Storey I, Cappa SF, Catricala E, et al. A 'Mini linguistic state examination' to classify primary progressive aphasia. Brain Commun. 2022;4:fcab299.
11. Epelbaum S, Saade YM, Flamand Roze C, Roze E, Ferrieux S, Arbizu C, et al. A reliable and rapid language tool for the diagnosis, classification, and follow-up of primary progressive aphasia variants. Front Neurol. 2021;11:571657.
12. Janssen N, Roelofs A, Van den BE, Eikelboom WS, Holleman MA, In de Braek DM, et al. The diagnostic value of language screening in primary progressive aphasia: validation and application of the Sydney language battery. J Speech Lang Hear Res. 2022;65:200-14.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
14. Monsch AU, Bondi MW, Salmon DP, Butters N, Thal LJ, Hansen LA, et al. Clinical validity of the Mattis dementia rating scale in detecting dementia of the Alzheimer type. A double cross-validation and application to a community-dwelling sample. Arch Neurol. 1995;52:899-904.
15. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982;140:566-72.
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
17. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529-36.

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REVIEW ARTICLE

Use of dexamethasone in patients with chronic subdural hematoma: a systematic review

Uso de dexametasona en pacientes con hematoma subdural crónico: una revisión sistemática

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Abstract

Background: *Chronic subdural hematoma (CSCH) is an old collection of blood and its degradation products in the subdural space, the treatment of choice in symptomatic patients is craniotomy, although it brings complications. The search for alternative therapies has increased, highlighting glucocorticoids, especially dexamethasone (DXM).* **Objective:** *To describe the efficiency, efficacy, and safety of the use of DXM in patients older than 18 years with CSCH in comparison with surgical drainage or placebo group.* **Method:** *Systematic review conducted according to PRISMA 2020 guidelines. Advanced searches were conducted in English and Spanish language, in the NEJM, PubMed and Embase databases through Cochrane Library using the descriptors and Boolean operators' "Dexamethasone" AND "Hematoma, Subdural, Chronic", and custom year range 2018-2023.* **Results:** *44 articles were found, of which, after discarding duplicates and applying the inclusion and exclusion criteria, only five articles were included.* **Conclusion:** *The review shows a positive impact on the risk of recurrence with the use of DXM in patients with CSDH; however, no conclusive results were found since this impact was only demonstrated in four of the five publications included. Likewise, the use of DXM in patients with CSDH is associated with an increased risk of complications and mortality, and no significant difference was demonstrated in functional outcomes and days of hospitalization compared to those who received primary surgery or placebo.*

Keywords: *Dexamethasone. Chronic subdural hematoma. Systematic review.*

Resumen

Antecedentes: *El hematoma subdural crónico (HSDC) es una colección antigua de sangre y de sus productos de degradación en el espacio subdural, el tratamiento de elección en pacientes sintomáticos es el de craneotomía, aunque trae consigo complicaciones. Se ha incrementado la búsqueda de terapias alternativas, destacando los glucocorticoides, en especial de la dexametasona (DXM).* **Objetivo:** *Describir la eficiencia, la eficacia y la seguridad del uso de DXM en pacientes mayores de 18 años con HSDC en comparación con el drenaje quirúrgico o un placebo.* **Método:** *Se realizó una revisión sistemática de acuerdo con las pautas PRISMA 2020 y se llevaron a cabo búsquedas avanzadas en idiomas inglés y español en las bases de datos NEJM, PubMed y Embase a través de Cochrane Library, utilizando los descriptores y operadores booleanos "Dexamethasone" AND "Hematoma, Subdural, Chronic", y con el rango de años 2018-2023.* **Resultados:** *Se encontraron 44 artículos, de los cuales, tras descartar duplicados y de aplicar criterios de inclusión y exclusión, solo se incluyeron cinco artículos.* **Conclusión:** *La revisión muestra un impacto positivo en el riesgo de recurrencia*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000021

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):96-105
www.archivosdeneurociencias.mx

con el uso de DXM en pacientes con HSDC; no obstante, los resultados no fueron concluyentes, ya que este impacto solo se demuestra en cuatro de las cinco publicaciones incluidas. Asimismo, está asociado a un mayor riesgo de complicaciones y mortalidad; además, no se demostró significancia en cuanto a resultados funcionales y días de hospitalización en comparación con los pacientes que recibieron cirugía primaria o placebo.

Palabras clave: *Dexametasona. Hematoma subdural crónico. Revisión sistemática.*

Introduction

Chronic subdural hematoma (CSDH) is one of the most common scenarios in the neurosurgery department. It was first described in *Carta III, Article 20, Sedibus* in 1761 by Morgagni[1,2]. It is defined as an old collection of blood and blood degradation products in the subdural space, usually occurring in old age and predominantly affecting males, with a 3:1 ratio, though it can occasionally present in young people and children[1,3,4]. The primary mechanism of this pathology is usually a traumatic event, but it can also be related to intracranial hypotension and coagulation defects[1], which are associated with increased use of anticoagulant and antiplatelet drugs. These drugs have been identified as a risk factor for the development of CSDH, along with advanced age, a history of falls, mild head injuries, hemorrhagic diatheses, alcohol use, epilepsy, and hemodialysis[3,5].

The incidence of CSDH ranges from 8.2 up to 14% per 100,000 inhabitants per year, with a mean age of 76.8 years. According to the World Health Organization, its incidence could double in the population older than 65 years between 2010 and 2050[3].

Surgical treatment is the choice for symptomatic CSDH patients, using 3 different approaches: minimal craniostomy (twist drill), craniotomy, and conventional craniostomy (burr-hole evacuation); the latter being the most widely used. However, the surgical approach carries multiple complications, including a high recurrence risk ranging from 9.2 up to 26.5%, with a need for reoperation in 10 up to 20% of cases, and morbidity and mortality rates of 16 and 6.5%, respectively[3,5]. Nonetheless, statistical data vary in the literature. Additionally, the procedure *per se* involves complications such as focal brain injury, acute postoperative subdural or intracranial hemorrhage, seizures, and surgical site infection, among others, as well as non-surgical complications related to the postoperative length of stay[6].

As a consequence, in recent years, the search for alternative therapies has increased, with interest in the use of glucocorticoids, particularly DXM, as a perioperative adjuvant or monotherapy in CSDH, given its anti-inflammatory and antiangiogenic effects, which can inhibit the formation of new blood vessels. This could positively impact shorter hospital stays and significantly reduce mortality, morbidity, and risk of recurrence[7].

In the last 10 years, the available evidence has been reviewed 5 times, searching for therapeutic alternatives to surgical treatment for patients with CSDH. These reviews found that the methodological approach includes various non-surgical alternatives, such as embolization of the middle meningeal artery, use of various steroids, administration of tranexamic acid, and use of atorvastatin as monotherapy or in combination with DXM. Only one of these shares variables with the present work, but it reviews publications up to 2017 without a specific reference to the initial period[8]. In contrast, this review is the result of an exhaustive search of the evidence from the last 5 years, focusing exclusively on the use of DXM as a perioperative adjuvant or monotherapy.

Considering the growing incidence of CSDH and the risks of the surgical approach, which is the treatment of choice, it is relevant to conduct a new systematic review to synthesize the most updated available scientific evidence on therapeutic alternatives, identify knowledge gaps, and reduce publication bias.

For this reason, the PICO methodology (Population, Intervention, Comparison, Outcome) was used to construct the research question: What is the efficiency, efficacy, and safety profile of using DXM in patients older than 18 years with CSDH vs surgical drainage or placebo? Thus, the primary endpoint of this study is to describe the efficiency, efficacy, and safety profile of using DXM in patients older than 18 years with CSDH vs surgical drainage or placebo.

Method

This systematic review was conducted following the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[9].

Eligibility criteria

Studies meeting the following criteria were included: 1) patients aged 18 years or older with a confirmed diagnosis of CSDH; 2) oral or IV DXM as monotherapy or adjuvant therapy; 3) articles within the year range of 2018 to July 2023; 4) documented outcomes such as mortality, recurrence rate, complications, adverse effects, length of stay, or functional outcome reporting using the Markwalder Grading Scale (MGS), modified Rankin Scale (mRS), or Glasgow Coma Scale (GCS); 5) the control group receiving surgical treatment or placebo. Excluded were protocols, letters to the editor, editorials, surveys, abstracts of original articles, pilot phase reports, summaries, and statistical analysis plans of original articles, as well as studies using another steroid besides DXM, use of atorvastatin, or any combination.

Information sources

Advanced searches were conducted across 3 different health sciences databases. The databases consulted were *The New England Journal of Medicine* (NEJM), covering from 1990 to present day; PubMed, covering from 1966 to present day; and Embase, through the Cochrane Library, with a temporal extension from 1947 to present day. The last search dates back to July 14th, 2023, for all databases.

Search strategy

The descriptors used in English, according to Medical Subject Headings (MeSH) 2023, were "dexamethasone" and "Hematoma, Subdural, Chronic," combined with Boolean operators as follows: "Dexamethasone" AND "Hematoma, Subdural, Chronic," with a custom year range from 2018 through 2023.

Data selection process

Two different researchers (AA and DA) independently reviewed the titles and abstracts of all retrieved articles according to the inclusion and exclusion criteria; the data were extracted into an Excel document. Subsequently, the same researchers examined the full texts of the included articles in pairs. In both examination processes, in case of disagreement, the inclusion was discussed between both researchers.

Assessment of the methodological quality of the studies

The Jadad scale, also known as the Jadad Score or Oxford Quality Scoring System, was used to assess the methodological quality of randomized clinical trials. The scale consists of five items related to blinding, randomization, and follow-up loss and is scored from 0 to 5 points. A higher score indicates greater methodological quality of the clinical trial evaluated, and if the score is < 3 points, the clinical trial is of poor quality[10] (Table 1).

Data mining process

The characteristics of the included articles were extracted into a table proposed by Merino-Trujillo[11] in 2013, recovering the following information: authors, article title, year of publication, intervention performed, analysis method, results, and findings. Additionally, the Jadad scale is included in the case of randomized clinical trials (Table 1).

Results

A total of 44 articles were found across the different databases, 12 of which were duplicates, and 32 were reviewed for title and abstract reading. After applying the inclusion and exclusion criteria, only 10 articles were selected for full-text review. Finally, 5 articles that met the inclusion criteria were included, as two could not be retrieved[12,13], one did not meet the outcome documentation[14], one administered DXM in combination with pantoprazole[15], and one did not have a control group[16] (Fig. 1). The results and findings of the included articles are shown in table 1.

Applying the Jadad scale, 1 study[17] scored 4 (good methodological value), 2 studies[18,19] scored 3 (medium methodological quality), and another[18] obtained a score of 1 (low methodological value).

The results of the included articles considered as predictors of the efficiency, efficacy, and safety profile of using DXM in patients with CSDH were mortality rates, recurrence, and complications, functional outcome reporting using MGS, mRS, or GCS, and the length of stay. Recurrence was indicated as a new blood collection in the subdural space, the presence of neurological symptoms and signs, or the need for additional surgery or therapy, as appropriate.

Miah et al.[20] in 2019, and Tariq and Bhatti[21] in 2021, reported lower recurrence and equal mortality rates

Table 1. Studies on the use of dexamethasone in patients with chronic subdural hematoma during the period 2019-2023

Authors and year	Title	Objective	Sample	Intervention	Analysis method	Results	OR (95%CI)	p	Findings	Jadad
Miah et al., 2019	Dexamethasone therapy in symptomatic chronic subdural hematoma (DECSA–R): a retrospective evaluation of initial corticosteroid therapy versus primary surgery	To evaluate the effect of primary surgery via burr hole craniostomy versus initial therapy with DXM	120 patients Cohort A: primary surgery (n = 60) Cohort B: initial DXM (n = 60)	In cohort A, 60 patients received primary surgery (without DXM as an adjunct), and 60 patients in cohort B started therapy with DXM	Retrospective evaluation of initial corticosteroid therapy versus primary surgery	Recurrence at 6 months Cohort A: 13/60 (22%) Cohort B: 7/60 (12%) Additional surgery after DXM Cohort B: 50/60 (83%) Reoperation Cohort A: 9/13 Cohort B: 7/7	2.11 (0.77-5.79)	0.15	No difference in clinical outcome is demonstrated in patients with symptomatic chronic subdural hematoma after initial therapy with DXM vs primary surgery	NA
						Complications Cohort A: 21 (35%) Cohort B: 33 (55%)	0.42 (0.20-0.89)	0.02		
						Mortality at 6 months 10% in both cohorts (6/60)	1.04 (0.29-3.76)	0.96		
						Favorable mRS score (0-3) at 3 months Cohort A: 37/53 (70%) Cohort B: 38/50 (76%)	NA			
						Good MGS score (0-1) at 3 months 96% in both cohorts				
						Length of stay (days) Cohort A: 10 Cohort B: 5	0.04 (0.00-0.66)	0.02		

(Continues)

Table 1. Studies on the use of dexamethasone in patients with chronic subdural hematoma during the period 2019-2023 *(continued)*

Authors and Year	Title	Objective	Sample	Intervention	Analysis method	Results	OR (95%CI)	p	Findings	Jadad
Mebberson et al., 2020	Prospective randomized placebo-controlled double-blind clinical study of adjuvant dexamethasone with surgery for chronic subdural hematoma with post-operative subdural drainage: interim analysis	Conduct the first prospective, randomized, placebo-controlled, registered study for DXM as an adjunct in chronic subdural hematoma surgery with post-operative subdural drainage	47 patients, 23 with DXM and 24 with placebo	Randomized 1:1 to receive placebo or a tapering DXM regimen for 2 weeks	Single-center, double-blind, prospective, randomized, placebo-controlled trial	Recurrence DXM: 0/23 (0%) Placebo: 5/24 (21%)	NA	0.049	No recurrences observed with DXM; only with placebo. No significant differences between groups in postoperative mortality and morbidity, length of stay, mRS, or adverse events. DXM administered as an adjunct in surgery with postoperative subdural drainage over a 2-week tapering regimen is safe and free of adverse effects	4
						Complications DXM: 9/23 (39%) Placebo: 6/24 (25%)		0.358		
						Mortality at 6 months DXM: 4/23 (17%) Placebo: 2/24 (8%)		0.415		
						Good mRS score (0-2) at 6 months DXM: 17/23 (74%) Placebo: 16/24 (66.6%)		0.81		
						Length of stay (days) DXM: 11.30 ± 6.0 Placebo: 18.92 ± 26.2		0.181		

(Continues)

Table 1. Studies on the use of dexamethasone in patients with chronic subdural hematoma during the period 2019-2023 *(continued)*

Authors and Year	Title	Objective	Sample	Intervention	Analysis method	Results	OR (95%CI)	p	Findings	Jadad
Hutchinson et al., 2020	Trial of dexamethasone for chronic subdural hematoma	To evaluate the effect of DXM on outcomes in patients with symptomatic chronic subdural hematoma: DXM would improve 6-month functional outcomes in patients with symptomatic chronic subdural hematoma by reducing the need for surgical interventions and hematoma recurrence after surgery	748 patients in total: 375 in the DXM group and 373 in the placebo group 45 patients (20 in the DXM group and 25 in the placebo group) withdrew consent to participate in the trial, and 23 patients were lost at the end. Finally, 341 in the DXM group vs 339 in the placebo group	Reduced 2-week course of oral DXM (8 mg twice daily on days 1-3, then 6 mg twice daily on days 4-6, then 4 mg twice daily on days 7-9, then 2 mg twice daily on days 10-12, and then 2 mg once daily on days 13-14) or equivalent placebo	Multicenter randomized trial in UK hospitals	Recurrence Post-surgery DXM: 6/349 (1.7%) Placebo: 25/350 (7.1%) Difference percentage (95%CI): –5.4 (–8.7 down to –2.5)	NA	DXM treatment resulted in fewer favorable outcomes than placebo at 6 months, but fewer repeat surgeries in patients receiving DXM. DXM was associated with more adverse events than placebo		3
						Complications Adverse events of interest DXM: 41/375 (10.9%) Placebo: 12/373 (3.2%)	3.4 (1.81-6.85)	< 0.001		
						Serious adverse events DXM: 60/375 (16.0%) Placebo: 24/373 (6.4%)	2.49 (1.54-4.15)	< 0.001		
						Mortality at 30 days DXM: 8/375 (2.1%) Placebo 2/373 (0.5%)	4.08 (1.01-27.2)	NA		
						Mortality at 6 months DXM: 30/341 (8.8%) Placebo 17/339 (5.0%)	1.83 (0.99-3.45)	NA		
						Favorable mRS outcome (0-3) at 3 and 6 months DXM: 268/322 (83.2%); 286/341 (83.9%) Placebo: 298/326 (91.4%); 306/339 (90.3%)	NA			

(Continues)

Table 1. Studies on the use of dexamethasone in patients with chronic subdural hematoma during the period 2019-2023 *(continued)*

Authors and Year	Title	Objective	Sample	Intervention	Analysis method	Results	OR (95%CI)	p	Findings	Jadad
Tariq et al., 2021	Adjunctive postoperative course of dexamethasone in chronic subdural hematoma: effect on surgical outcome	Compare the effect of burr hole craniostomy with and without a postoperative course of DXM on the recurrence rate of chronic subdural hematoma (CSDH)	92 patients randomized into 2 groups of 46 patients each	Group 1: 16 mg preoperative DXM, followed by evacuation via surgery. DXM was then tapered over 15 days in total Group 2: evacuation via surgery, did not receive DXM	Controlled, randomized, prospective trial	Recurrence Group 1: 1 (2.2%) Group 2: 2 (4.3%)	NA	0.557	Neurological and radiological outcomes and mortality rates were similar in both groups. The recurrence rate was lower and the complication rate higher in the DXM group, but without statistical significance	1
						Complications Group 1: 27 (58.7%) Group 2: 20 (43.5%) Mortality reported as a complication Mortality Group 1: 1 (2.2%) Group 2: 1 (2.2%)		0.535		
Miah et al., 2023	Dexamethasone vs surgery for chronic subdural hematoma	Compare DXM as a standalone treatment and surgical evacuation for symptomatic chronic subdural hematoma	252 patients (77% male) from a planned sample size of 420: 127 with DXM and 125 with surgery	DXM: a 19-day tapering course (8 mg every 12 h on days 1-4, tapering to half every 3 days until 0.5 mg daily on day 19 and discontinued on day 20). Surgery (hematoma evacuation with a burr hole, followed by the insertion of a subdural drain for 2 days) was scheduled within 7 days of randomization + control CT scan at 2 weeks after treatment initiation	Randomized, multicenter trial designed according to PROBE, conducted in 12 hospitals in the Netherlands	Recurrence Additional surgery DXM: 70/127 (55.1%) Surgery: 8/125 (6.4%)	17.96 (8.09-39.85)	NA	55% of patients in the DXM group eventually underwent surgery compared to 6% in the surgery group who underwent a new operation. More patients died in the DXM group than in the surgery group, and patients in the DXM group had more complications and longer hospital stays than those in the surgery group	3
						Recurrence Additional therapy DXM: 77/127 (60.6%) Surgery: 21/125 (16.8%)	3.14 (1.93-5.12)	NA		
						Complications Adverse events DXM: 144 events Surgery: 89 events Serious adverse events DXM: 102 events Surgery: 65 events	NA			
						Mortality DXM: 8/127 (6.3%) Surgery: 2/125 (1.6%)	2.63 (0.43-16.67)	NA		
						Favorable mRS outcome (0-3) at 3 months DXM: 104/127 (82%) Surgery: 110/125 (88%)	0.55 (0.34-0.90)	NA		
						Hospital days DXM: 12.0 ± 10.6 Surgery: 6.8 ± 6.7	5.20 (3.00-7.40)	NA		

DXM: dexamethasone; 95%CI: 95% confidence interval; MGS: Markwalder Grading Scale; mRS: modified Rankin Scale; NA: not applicable; OR: odds ratio; PROBE: Prospective Randomized Open Blinded End-Point.
Source: Own elaboration.

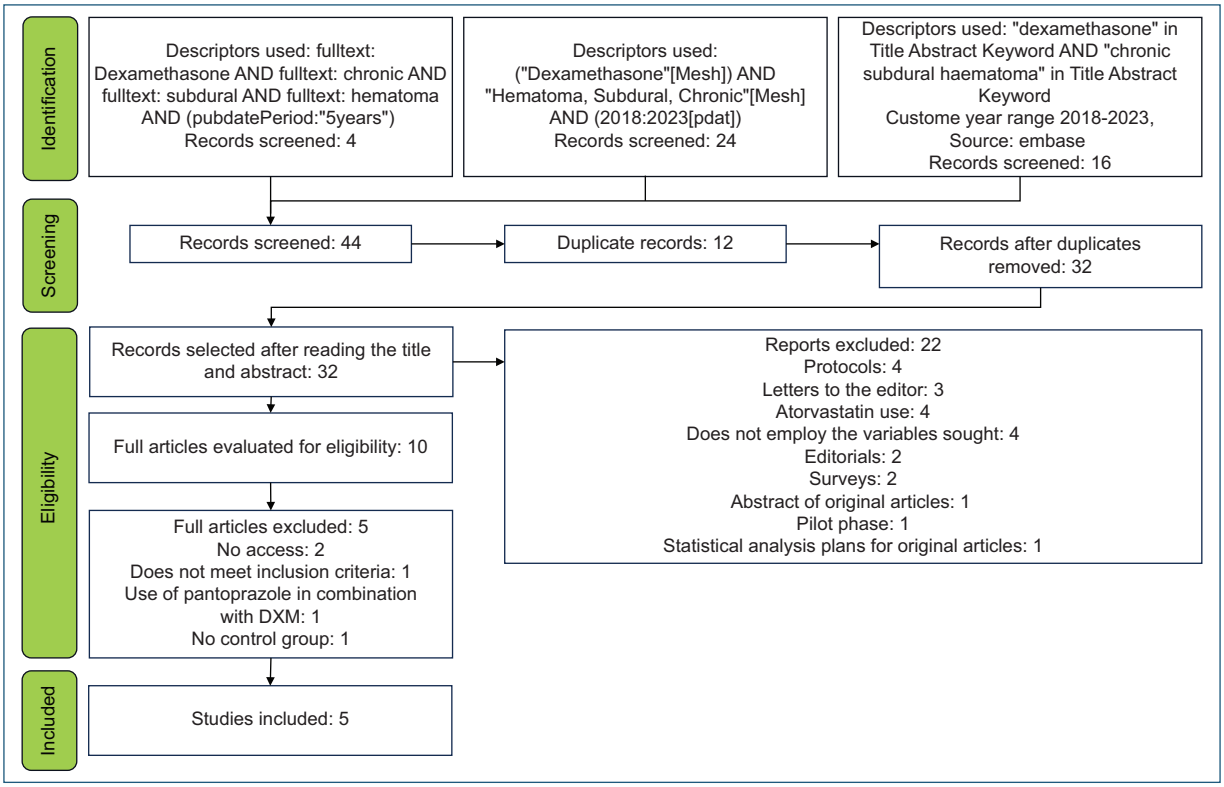

Figure 1. PRISMA flow diagram on the use of dexamethasone in patients with chronic subdural hematoma.

in the DXM group vs patients undergoing primary surgery. Miah et al.[19] in 2023 also used patients undergoing primary surgery as a control group but found higher recurrence and mortality in the DXM group. On the other hand, in the studies by Mebberson et al.[17] in 2020 and Hutchinson et al.[18] in 2020, DXM showed lower recurrence but higher mortality rates vs placebo. Regarding complications, all studies reported a higher incidence in the DXM group regardless of the control group treatment. Additionally, no significant difference was found in the functional outcomes of patients receiving DXM, surgery, or placebo. It is noteworthy that Mebberson et al.[17] and Tariq et al.[21] evaluated the use of DXM as a perioperative adjuvant; despite this, no difference was found in the study outcomes where DXM was evaluated as potential monotherapy.

Length of stay was reported only by Miah et al.[20], Mebberson et al.[17], and Miah et al.[19], and in the first two, DXM had a shorter hospital stay compared to primary surgery and placebo, respectively, while in the study by Miah et al.[20], a longer hospital stay was reported for patients who received DXM.

Discussion

As mentioned earlier, the interest in using glucocorticoids, in this case, DXM, in patients with CSDH stems from the aim to reduce hospitalization time, mortality, morbidity, and the risk of recurrence[7]. However, the findings show that the use of DXM in patients with CSDH is associated with a higher risk of complications and mortality. The most widely reported complications in the DXM group across the evaluated studies include hyperglycemia, infections, and delirium. Other reported complications include subdural empyema[19,20], thromboembolic events, seizures, hypoglycemia, cardiac complications[20], hyponatremia, pneumonia, wound leakage, atrial fibrillation, fluid overload[17], new-onset diabetes and psychosis[18], pneumocephalus, and iatrogenic parenchymal injury[20]. Additionally, there was no significant difference in functional outcomes vs primary surgery or placebo. Regarding hospitalization time, the results are inconsistent, as only 3 articles reported this outcome, and not all had the same conclusion (Table 1).

The evidence shows that DXM only positively impacts the risk of recurrence in 4 of the 5 included articles. The differing results regarding both recurrence and hospitalization time are from the study by Miah et al.[19],

which contradicts previous findings and raises questions about what other authors have previously reported, as it is the most recent article included.

Additionally, Hutchinson et al.[18] enrolled patients for randomization regardless of whether they had undergone surgical drainage or were scheduled for surgery during the study period, which prevented firm conclusions about the effect of DXM as a conservative management method to avoid surgery. In two other studies, patients were subjected to a DXM regimen as a perioperative adjuvant; in the results by Mebberson et al.[17], a benefit in recurrence risk can be affirmed, but not for the findings reported by Tariq et al.[21], as 83% of the patients underwent additional surgery after DXM, contradicting their initial report of lower recurrence with DXM. Finally, in the studies conducted by Miah et al.[19-21], patients in the DXM group did not receive surgery, but the results were contrary to the recurrence.

On the other hand, it is important to note the findings of Holl et al.[16] in 2022, which show that medical judgment plays a role in the initial treatment decision for patients with CSDH. This study aimed to identify patient characteristics associated with the need for additional surgery in those treated primarily with DXM (recurrence) and found that those treated with surgery more frequently had a Markwalder score of 2, used statins, had a larger midline shift, a thicker hematoma, and presented with bilateral or separated hematomas. These findings may suggest that the factors predisposing to recurrence risk are not inherent to the treatment used, but rather to the individual characteristics of the patient, according to the researchers.

Considering that the analysis of the benefit of DXM regarding recurrence risk does not yield conclusive results, and given the findings in reports of complications, mortality, length of stay (days), and functional outcomes, it cannot be associated with superior or non-inferior efficacy, efficiency, or safety for the use of DXM as monotherapy or perioperative adjuvant.

Conclusions

According to the reviewed studies, the use of DXM in patients with CSDH shows a positive impact on recurrence risk, but the results are not conclusive, as this impact is only demonstrated in four of the five included publications. Likewise, the use of DXM in patients with CSDH is associated with a higher risk of complications and mortality, and no significant difference in functional outcomes or hospitalization days was demonstrated compared to primary surgery or placebo.

Therefore, it is important to emphasize the significance of decision-making and the involvement of the medical team in the management of patients with CSDH, taking into account patient characteristics at the time of admission, during hospitalization, and functional outcomes at discharge, being aware of the internal and external factors that may impact the patient's quality of life.

Acknowledgements

We deeply wish to thank Narce D. Reyes Pérez, who supported, advised, and encouraged us in the completion of this work; without her help, this would not have been possible.

Authors' contributions

A. Ayala and D. Alcaraz were responsible for the conceptualization, data curation, formal analysis, research, methodology, project administration, resources, software, visualization, and drafting of the original manuscript. Narce Dalia Reyes Pérez was involved in the process of supervision, writing, review, and editing of the final document.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that no patient data appear in this article. In addition, the authors have recognized and followed the recommendations according to the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of

generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables or their corresponding captions or legends.

References

1. Yadav YR, Parihar V, Namdev H, Bajaj J. Chronic subdural hematoma. Asian J Neurosurg. 2016;11:330-42.
2. Dammers R, Holl DC, Kapiteijn B, Kompanje EJO. The first historical description of chronic subdural hematoma: a tale of inaccurate interpretation, inaccurate quoting and inaccurate requoting. J Hist Neurosci. 2023;32:1-18.
3. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. Nat Rev Neurol. 2014;10:570-8.
4. Ramachandran R, Hegde T. Chronic subdural hematomas — causes of morbidity and mortality. Surg Neurol. 2007;67:367-72.
5. Gascón Cerda G, Salazar Pérez NJ, Sandoval Bonilla BA, Sikahall Meneses E, Torres Arreola LP. Guía de práctica clínica. Diagnóstico y tratamiento del hematoma subdural crónico tarumático en pacientes mayores de 18 años de edad. México: Instituto Mexicano del Seguro Social; 2009. (Consulted: 09-07-2023.) Available in: https://www.imss.gob.mx/sites/all/statics/guiasclinicas/179GER.pdf.
6. Viaroli E, Iaccarino C, Maduri R, Thomas Daniel R, Servadei F. Complications After Surgery for Chronic Subdural Hematomas. In: Nanda A, editor. Complications in Neurosurgery. Philadelphia: Elsevier; 2019. p. 274-279.
7. Fountas K, Kotlia P, Panagiotopoulos V, Fotakopoulos G. The outcome after surgical vs nonsurgical treatment of chronic subdural hematoma with dexamethasone. Interdisciplinary Neurosurgery. 2019;16:70-4.
8. Yao Z, Hu X, Ma L, You C. Dexamethasone for chronic subdural haematoma: a systematic review and meta-analysis. Acta Neurochir (Wien). 2017;159:2037-44.
9. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
10. Cascaes da Silva F, Valdivia Arancibia BA, da Rosa Iop R, Barbosa Gutierres Filho PJ, da Silva R. Escalas y listas de evaluación de la calidad de estudios científicos. Rev Cuba Inf Cienc Salud. 2013;24:295-312.
11. Merino-Trujillo A. Como escribir documentos científicos (Parte 3). Artículo de revisión. Salud en Tabasco. 2011;17:36-40. Available in: https://www.redalyc.org/articulo.oa?id=48721182006.
12. Diener HC. Dex-CSDH trial: dexamethasone for chronic subdural hematoma. Arzneimitteltherapie. 2021;39:84-5.
13. Miah IP, Holl DC, Bruggink T, Peul WC, Tolman C, Walchenbach R, et al. Dexamethasone therapy versus surgery for chronic subdural haematoma, a clinical randomised controlled trial (DECSA-trial). Eur J Neurol. 2018;25:389.
14. Edlmann E, Giorgi-Coll S, Thelin EP, Hutchinson PJ, Carpenter KLH. Dexamethasone reduces vascular endothelial growth factor in comparison to placebo in post-operative chronic subdural hematoma samples: a target for future drug therapy? Front Neurol. 2022;13:952308.
15. Miah IP, Blanter A, Tank Y, van Zwet EW, Rosendaal FR, Peul WC, et al. Change in hematoma size after dexamethasone therapy in chronic subdural hematoma subtypes: a prospective study in symptomatic patients. J Neurotrauma. 2023;40:228-39.
16. Holl DC, Fakhry R, Dirven CMF, te Braake FAL, Begashaw OK, Moudrous W, et al. Surgery after primary dexamethasone treatment for patients with chronic subdural hematoma — a retrospective study. World Neurosurg. 2022;162:e358-68.
17. Mebberson K, Colditz M, Marshman LAG, Thomas PAW, Mitchell PS, Robertson K. Prospective randomized placebo-controlled double-blind clinical study of adjuvant dexamethasone with surgery for chronic subdural haematoma with post-operative subdural drainage: interim analysis. J Clin Neurosci. 2020;71:153-7.
18. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, et al. Trial of dexamethasone for chronic subdural hematoma. N Engl J Med. 2020;383:2616-27.
19. Miah IP, Holl DC, Blaauw J, Lingsma HF, den Hertog HM, Jacobs B, et al. Dexamethasone versus surgery for chronic subdural hematoma. N Engl J Med. 2023;388:2230-40. Available from: https://pubmed.ncbi.nlm.nih.gov/37314705
20. Miah IP, Herklots M, Roks G, Peul WC, Walchenbach R, Dammers R, et al. Dexamethasone therapy in symptomatic chronic subdural hematoma (DECSA–R): a retrospective evaluation of initial corticosteroid therapy versus primary surgery. J Neurotrauma. 2020;37:366-72.
21. Tariq J, Bhatti SN. Adjunctive postoperative course of dexamethasone in chronic subdural hematoma: effect on surgical outcome. Pak J Med Sci. 2021;37:1877.

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CASE REPORT

Parkinsonism as a manifestation of secondary syphilis

Síndrome parkinsoniano como manifestación de sífilis secundaria

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Abstract

Neurosyphilis is defined as the affection of the central nervous system due to the presence of Treponema pallidum. The most common neurological manifestations of the disease include meningitis, tabes or dementia. We report the case of a 57-year-old male who presents with Parkinson-like symptoms. Some months later he develops a rash, and the diagnosis of neurosyphilis is confirmed after a positive VDRL is found on serum and cerebrospinal fluid. After antimicrobial treatment, there is improvement of the Parkinson-like symptoms, which confirms the relationship between the neurological manifestations and the infection.

Keywords: *Neurosyphilis. Parkinsonism. Syphilis.*

Resumen

La neurosífilis se define como la afectación del sistema nervioso central por Treponema pallidum. Sus manifestaciones neurológicas más frecuentes son meningitis, tabes o demencia. Presentamos el caso de un hombre de 57 años que debuta con presencia de síntomas parkinsonianos. Unos meses después presenta un exantema y es diagnosticado con neurosífilis mediante VDRL positivo en sangre y líquido cefalorraquídeo. Después de recibir tratamiento antimicrobiano muestra mejoría del síndrome parkinsoniano, lo cual confirma la relación entre las manifestaciones neurológicas y la infección.

Palabras clave: *Neurosífilis. Parkinsonismo. Sífilis.*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000023

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):106-109
www.archivosdeneurociencias.mx

Introduction

Neurosyphilis is an infection of the central nervous system (CNS) due to *Treponema pallidum* infection[1]. Since the advent of antibiotics, the prevalence and incidence of this disease have decreased significantly. The World Health Organization mentions that in 2020 there was an incidence of 7.1 million cases worldwide in both sexes[2].

Syphilis can affect the nervous system in different ways. It may present early as asymptomatic meningitis, symptomatic meningitis, or meningovascular disease, while the main late neurological signs are dorsal tabes and paralytic dementia[3]. Syphilis diagnosis is typically established through treponemal or non-treponemal tests in serum, but diagnosing neurosyphilis requires confirmation of a positive VDRL (venereal disease research laboratory) test in cerebrospinal fluid (CSF). The U.S. Centers for Disease Control and Prevention recommend performing a lumbar puncture in patients with syphilis in the following cases[3]:

– Neurological or otological symptoms at any stage of the infection.
– Evidence of tertiary syphilis elsewhere in the body.
– Treatment failure at any stage of the infection.

Once neurosyphilis has been diagnosed, treatment with crystalline penicillin G, 18-24 million units per day for 10-14 days, is advised. To confirm treatment response, normalization of the CSF cell count must be verified. Protein and VDRL values may remain abnormal for a long time. If cell count has not dropped after 6 months, or proteins and VDRL have not normalized after 2 years, retreatment should be considered[4].

We present the case of a 57-year-old man who exhibited parkinsonian symptoms due to *T. pallidum* infection, with improvement in neurological signs following antimicrobial treatment.

Case report

Background

Mother deceased at 80 years old with a diagnosis of Alzheimer's disease, and father deceased at 75 years old from acute myocardial infarction. A paternal uncle has been diagnosed with Parkinson's disease. Positive smoking history from age 20 to 50 at 20 cigarettes per day. Alcohol dependence, rehabilitated 15 years ago. Engages in frequent physical activity and has an active sex life with 2 partners. Pneumonia due to SARS-CoV-2 in May, 2020.

Current illness

He first visited the neurology clinic on July 5th, 2020, reporting clumsiness and tremor in the right hand that hinder daily activities, as well as a sensation of lack of control over the position of the right foot while running, with frequent tripping. He also complains of "mental clumsiness" and some slowness in decision-making at work. Objective assessment confirmed the presence of extrapyramidal symptoms, without meeting clear criteria for Parkinson's disease. On the Unified Parkinson's Disease Rating Scale (UPDRS), he scored 22 points; on the Folstein Mini-Mental State Examination, 29; on the MoCA, 27; on the Beck Depression Inventory (BDI-II), 16; and on the Hamilton Anxiety Scale (HAM-A), 22 points. The diagnosis of parkinsonism, along with depression and anxiety, was made, and treatment with escitalopram (10 mg per day) was initiated, with a recommendation for physical rehabilitation. Management with dopaminergic drugs was deferred.

On a follow-up visit on October 15th, 2020, the patient reported improvement in cognitive and motor symptoms, although tremor in the right hand persisted during daily activities. A third visit in March, 2021, showed stability of symptoms.

On December 5th, 2021, the patient was admitted to the ER due to increased difficulty performing activities such as dressing or eating with the right hand over the past 2 weeks, as well as several falls due to clumsiness in the feet. He mentioned that in the last month he had been receiving dermatological treatment for dermatitis in the perianal region, classified as contact dermatitis.

Physical examination

Vital signs were within normal parameters. The patient was alert, oriented, cooperative, with normal language. Mini-Mental State Examination score was 29 points and UPDRS score was 22 points. Fundoscopy and cranial nerves were normal. Generalized strength was 5/5, osteotendinous reflexes were normal, with rigidity and bradykinesia in all 4 limbs. Gait showed dystonia in eversion of the right foot. Plantar response was bilaterally flexor. The Romberg sign was positive. No meningeal signs were found.

Supplementary tests

Brain MRI ruled out evident structural lesions (Fig. 1). A lumbar puncture with CSF cytochemical analysis showed the following results: cells 0 (0-1/mm^3), proteins

32 mg/dL (15-45 mg/dL), and glucose 76 mg/dL (serum 98 mg/dL). The VDRL test in blood and CSF turned out positive.

Diagnosis

Based on the lumbar puncture findings, a diagnosis of neurosyphilis was established, and treatment with crystalline penicillin G, 24 million units per day IV for 14 days, was initiated.

Course of the disease

Three months after the completion of antibiotic treatment, the VDRL test was negative in serum. The patient reported improvement in parkinsonian symptoms and gait, which was confirmed objectively in the physical examination. At this time, the UPDRS score was 15 points. A new consultation in June, 2022, showed persistent improvement in neurological symptoms, with a UPDRS score of 5 points (Fig. 2).

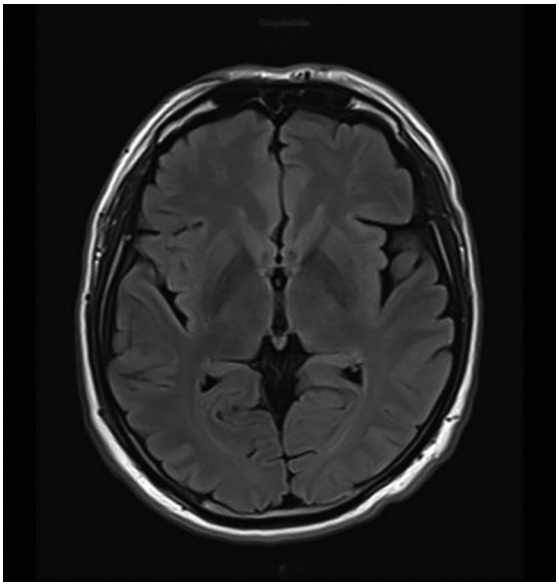

Figure 1. Simple MRI performed on September 5th, 2021. In the TI phase, no evident structural disorders are seen.

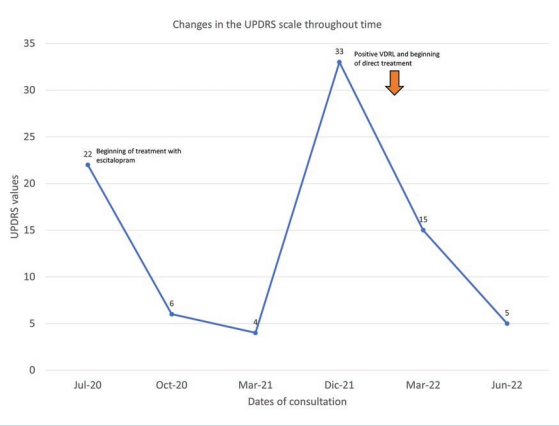

Figure 2. Progression of UPDRS throughout time. It is noted that, after initiating pharmacological treatment with escitalopram, the scores decrease significantly. In December 2021, there was an increase in the score. Once the diagnosis of neurosyphilis was confirmed and treatment with crystalline penicillin G was received, the scale score decreased drastically again.

Discussion

Classic neurological signs of syphilis include meningovascular syphilis, dorsal tabes, and syphilitic dementia. The association of neurosyphilis and parkinsonian symptoms is rare. It has been proposed that parkinsonism associated with syphilis occurs due to alteration of dopaminergic structures, creating a functional parkinsonism environment. There are case reports in which syphilis may have exacerbated symptoms in patients with pre-existing Parkinson's disease or triggered parkinsonian symptoms due to an inflammatory process affecting basal ganglia or other midbrain structures[5]. Additionally, it has been observed that antimicrobial treatment may reverse parkinsonian signs in some cases[6]. There are few reports of parkinsonian symptoms due to neurosyphilis; only 1% of patients with atypical Parkinson's symptoms can be attributed to an infectious origin[7]. Neurosyphilis is sometimes referred to as "the great imitator" due to its lack of a specific clinical picture and its ability to mimic other conditions. It has been found that the most widely associated symptom is cognitive impairment, while parkinsonian symptoms are not commonly reported[8].

Infections are among the possible etiologies of Parkinson's disease. Unlike idiopathic etiology, infectious causes present symptoms more rapidly[9]. Possible viral causes of Parkinson's disease include influenza viruses, herpes simplex virus 1, Epstein-Barr virus, varicella-zoster virus, hepatitis C virus, Japanese encephalitis virus, West Nile virus, and human immunodeficiency virus (HIV)[9]. Among bacterial agents, a case potentially associated with *Helicobacter pylori* has been reported[9]. These pathogens produce neuroinflammation through microglial activation and the release of pro-inflammatory factors (tumor necrosis factor-alpha, interleukins 6 and 1β) that damage dopaminergic neurons. These factors lead

to a continuous cycle of chronic inflammation and neuronal damage[9].

In the absence of a clear history of sexually transmitted diseases or primary syphilis signs, diagnosing neurosyphilis can be challenging. Although neurosyphilis is widely reported to occur years after infection, it can appear at any stage of the disease[1].

Our patient showed improvement in UPDRS scores following escitalopram administration. This may be due to the fact that several items on this scale include disorders in thinking, depression, and motivation-initiative, which are also assessed in scales specifically for evaluating parkinsonism[10]. After administering this medication, the patient showed improvement in cognitive symptoms and a slight improvement in motor symptoms, which is consistent with the currently available literature.

While there are cases of parkinsonian symptoms due to tertiary syphilis or congenital syphilis, the incidence of these disorders has decreased significantly due to the availability of antibiotics[11]. As seen in this patient, cases of parkinsonism associated with syphilis still occur, even in the secondary phase of the disease. Although it is often thought that this neurological sign is rather associated with tertiary syphilis it is important to highlight that CNS involvement can occur at any stage of the infection.

Conclusions

Despite the increasing use of antibiotics and awareness of safe sexual practices, sexually transmitted diseases continue to exist, and their complications, such as neurosyphilis, still occur. As demonstrated in this case, in patients with atypical parkinsonian symptoms, rapid deterioration, or in association with dermatological lesions, it is important to consider the possibility of syphilis. Timely treatment is crucial to favor clinical regression.

Funding

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

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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

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

References

1. Galindo J, Mier JF, Miranda CA, Rivas JC. Neurosífilis: un problema antiguo que no pierde actualidad. Rev Colomb Psiquiatr. 2017;46:69-76.
2. Organización Mundial de la Salud. Estrategias mundiales del sector de la salud contra el VIH, las hepatitis víricas y las infecciones de transmisión sexual para el periodo 2022-2030. OMS; 2022. Available in: https://www.who.int/es/publications/i/item/9789240053779#:~:text=Las%20estrategias%20mundiales%20del%20sector,sida%2C%20las%20hepatitis%20v%C3%ADricas%20B.
3. Stokes JH. Modern clinical syphilology: diagnosis – treatment – case studies. JAMA. 1927;88:589-90.
4. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(RR-03):1-137.
5. McAuley J, Hughes G. Neurosyphilis presenting as parkinsonism. BMJ Case Rep. 2015;2015:bcr2015210277.
6. Sandyk R. Parkinsonism secondary to neurosyphilis. A case report. S Afr Med J. 1983;63:665-6.
7. Rissardo JP, Caprara ALF. Parkinsonism-plus syndrome secondary to neurosyphilis: case report and literature review. Neurol India. 2022;70:1635-8.
8. Liis S, Mark B, Pille T. Neurosyphilis as a great imitator: a case report. BMC Res Notes. 2016;9:372.
9. Limphaibool N, Iwanowski P, Holstad MJV, Kobylarek D, Kozubski W. Infectious etiologies of parkinsonism: pathomechanisms and clinical implications. Front Neurol. 2019;10:652.
10. Chen J, Xu P, Guo X, Zou T. Comparative analysis of the effects of escitalopram, pramipexole, and transcranial magnetic stimulation on depression in patients with Parkinson disease: an open-label randomized controlled trial. Clin Neuropharmacol. 2022;45:84-8.
11. Spitz M. Parkinsonism secondary to neurosyphilis. Mov Disord. 2008;23:1948-9.

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CASE REPORT

Thoracic spinal cord trauma: an adequate functional outcome with timely surgical management

Traumatismo raquimedular torácico: un resultado funcional adecuado con manejo quirúrgico oportuno

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Abstract

Spinal cord trauma can be a devastating injury for the trauma patient, being associated with high mortality rates and significant morbidity. Fracture of the cervical spine is the most common, followed by the thoracolumbar region, but thoracolumbar fracture-dislocations are less frequent. Most of these types of fracture-dislocations at the thoracic level are associated with severe spinal cord injury and complete neurological deficit. Female patient with a fracture at the level of T6-T7 secondary to a fall of 3 meters after motorcycle skid. On physical examination, 4/5 pelvic limbs were strong, with no other neurological deficit. Computed tomography and magnetic resonance imaging show a fracture due to a translation and rotation mechanism, causing injury to both the anterior elements and the posterior ligament complex, accompanied by a sternal fracture that required conservative management, which is why it is classified as a type C of the AOSpine at the level of T6-T7, treated with posterolateral fixation. Fractures-dislocation at the thoracic level are rare and require surgical management due to the instability and neurological deficit that they may present. Timely surgical treatment avoids permanent neurological sequelae and leads to better neurological recovery.

Keywords: *Spinal cord injuries. Thoracolumbar fracture. TLICS. Posterolateral fixation.*

Resumen

El trauma raquimedular puede ser una lesión devastadora para el paciente traumático, asociándose a altas tasas de mortalidad y una morbilidad significativa. La fractura de columna cervical es la más común, seguida de la región toracolumbar, pero las fracturas-luxaciones toracolumbares son mucho menos frecuentes. Este tipo de fractura-luxación torácica se asocia con lesión grave de la médula espinal y déficit neurológico completo. Mujer con fractura-luxación a nivel T6-T7 secundaria a una caída de tres 3 metros posterior a derrape en motocicleta. En la exploración física con fuerza en miembros pélvicos 4/5, sin otro déficit neurológico. La tomografía computarizada y la resonancia magnética evidencian una fractura por mecanismo de traslación y rotación, causando lesión tanto de elementos anteriores como del complejo ligamentario posterior, acompañada de fractura esternal que requirió manejo conservador, motivo por el cual se cataloga como tipo C de la AOSpine a nivel de T6-T7 y es tratada con fijación posterolateral. Las fracturas-luxaciones a nivel torácico son raras y requieren manejo quirúrgico debido a la inestabilidad y el déficit neurológico que pueden llegar a presentar. El tratamiento quirúrgico oportuno evita secuelas neurológicas permanentes y conduce a una mejor recuperación neurológica.

Palabras clave: *Traumatismo raquimedular. Fractura toracolumbar. TLICS. Fijación posterolateral.*

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000024

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):110-114
www.archivosdeneurociencias.mx

Introduction

Spinal cord injury (SCI) should be suspected in victims of high-speed traffic accidents[1]. A systematic review was conducted through the PubMed, Embase, and Cochrane databases on SCI studies published between 2000 and 2016, reporting a global incidence of 10.5 cases per 100,000 people. This resulted in an estimated 768,473 to 790,695 cases of SCI worldwide each year. Men are more commonly affected by SCI[2].

SCI most frequently occurs in the cervical spine. Traffic accidents are the most common mechanisms of SCI worldwide, accounting for 41.6% of all SCI cases. Mortality rates attributed to SCI range from 0 up to 60%[2].

In Mexico, the mean age of 38 years seems to be at the highest risk for SCI, most occurring in men. The main etiology is falls from a considerable height, and most patients present with thoracic SCI[3].

Approximately 50 up to 60% of thoracolumbar injuries affect the transition levels (T11-L2) and 25 up to 40% affect the thoracic spine[4].

Case report

A 37-year-old woman with uncontrolled diabetes mellitus was admitted to the ER after a motorcycle accident, followed by a skid and a fall into a 3-meter-deep ravine. On physical examination, she had a Glasgow Coma Scale score of 15, with intact higher mental functions and cranial nerves. Motor: normotonic, normotrophic, with strength in C4, C5, C6, C7, C8, and T1 rated as 5/5 bilaterally on the Daniels scale, and L2, L3, L5, L5, and S1 rated as 4/5 bilaterally on the Daniels scale, with preserved sensation in both anterior and posterior columns, classified as ASIA D. Computed tomography and magnetic resonance imaging of the thoracolumbar spine revealed a fracture by a translation and rotation mechanism, causing injury to anterior elements, the wall, and the posterior tension band, classified as T6-T7: C N3 M2 by the AOSpine classification (Fig. 1), as well as a sternal fracture assessed by the thoracic team, who recommended conservative management.

Discussion

Mechanical stability is a critical factor in decision-making. TLICS is a classification scale for thoracolumbar injuries that combines injury morphology, assessment of relevant mechanical stability for the posterior ligamentous complex, and neurological status[1]; a total score > 5 indicates surgical management[1].

AOSpine classifies thoracolumbar spine fractures according to their morphology into 3 types:

- Type A: caused by a compression mechanism affecting the anterior elements.
- Type B: caused by a traction mechanism, affecting the tension band.
- Type C: caused by a rotation-translation mechanism, causing injury to both anterior and posterior elements.

According to this classification, types A4, B1, B2, B3, and C injuries require surgical stabilization[5].

McCormack introduced a classification intended solely to identify fractures requiring supplemental anterior fixation after posterior surgery[5,6].

White and Panjabi stated that a stable spine is capable, under physiological load, of maintaining normal movement so that there is no initial or additional neurological deficit, significant deformity, or disabling pain. They also developed a checklist for thoracic instability[7] (Table 1). The patient's TLICS (Thoracolumbar Injury Classification and Severity Score) scores were as follows: injury morphology 3 points, posterior ligamentous complex 3 points, and neurological status (spinal cord injury) 2 points. The overall TLICS score was 8 points, indicating surgical treatment, with a McCormack score of 6 requiring a posterior approach, and a White and Panjabi score of 10 indicating an unstable spine requiring surgical management. The patient underwent posterior approach surgery with fluoroscopic guidance, laminectomy at T6-T7, placement of transpedicular screws in T4-T5 and T8-T9, and manual distraction of the spinous process of the vertebrae proximal and distal to the fracture site, using forceps for fracture reduction, followed by fixation with lateral bars and locks to maintain reduction (Fig. 2). The surgical procedure was performed 8 hours after her admission. The immediate postoperative status was ASIA E, without neurological deficit. She had an uncomplicated hospital stay and was discharged 2 days after the surgery. Six months later, she showed full neurological recovery.

Intravenous methylprednisolone for neuroprotection and reduction of secondary injuries remains a controversial topic in SCI. No long-term benefits have been demonstrated beyond 6 months. The NASCIS I and II studies failed to show a clinically significant improvement

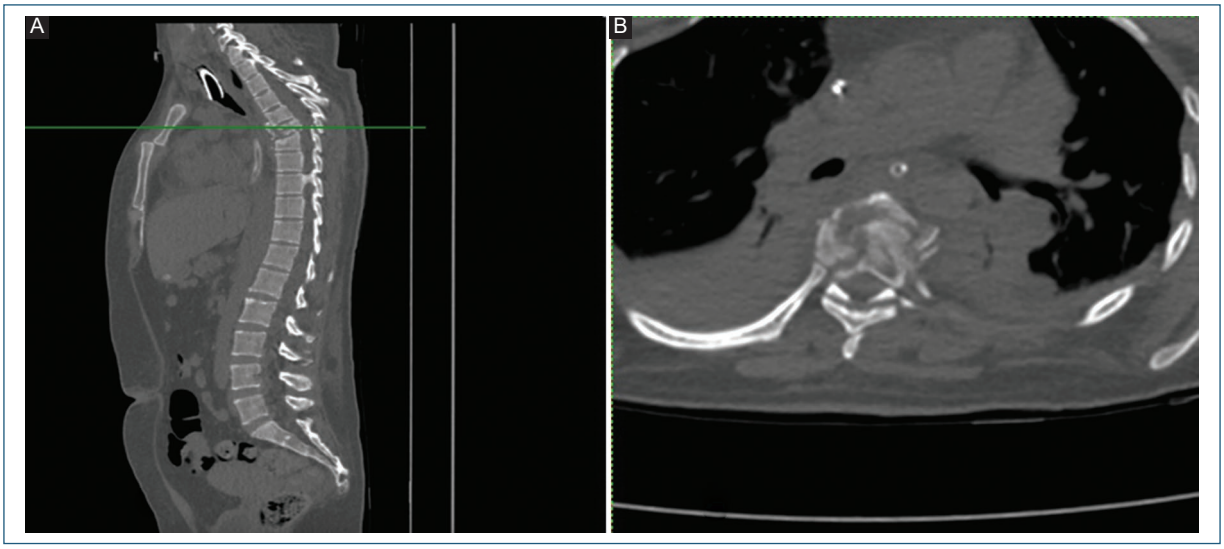

Figure 1. A: simple sagittal computed tomography (CT) view of the spine showing a fracture-dislocation at T6-T7 level and a sternal manubrium fracture that required conservative management. **B:** axial CT showing a fracture of all 3 Denis columns at T6 level.

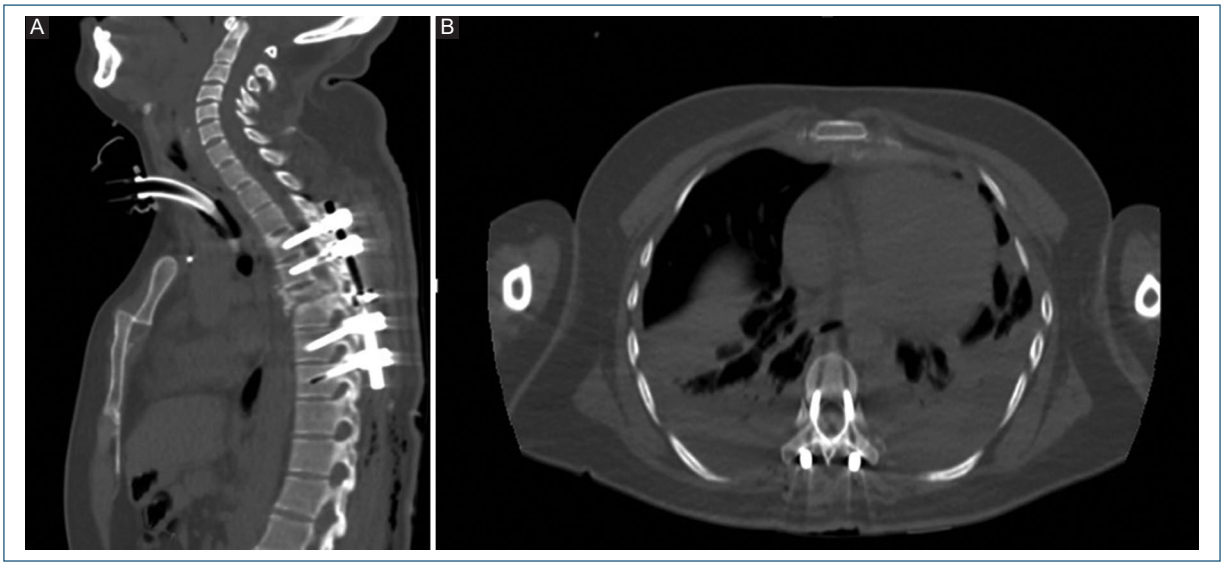

Figure 2. A: sagittal CT view of the spine post-surgery showing the results after laminectomy at T6-T7 with subsequent placement of transpedicular screws at T4-T5 and T8-T9, and open reduction of the fracture-dislocation. **B:** axial CT view of the spine at T5 level showing correct placement of the transpedicular screw.

and increased the risks of wound infection and gastrointestinal hemorrhage. NASCIS III compared 24-hour vs 48-hour methylprednisolone infusion, and a trend was observed toward a higher incidence of severe pneumonia in patients who received the 48-hour infusion and a potential increase in severe sepsis. Therefore, steroids are not recommended in SCI[8].

In this case, the patient behaved similarly to what is reported in the literature, as motor vehicle accidents are the most common cause of SCI[9], and thoracic fractures are the most common type, with fracture-dislocations being rare[10,11].

Early fixation is preferred in patients with thoracic spine fractures because it allows early mobilization and reduces the incidence of pneumonia. Fixation within 72

Table 1. Classification and scoring of thoracolumbar injuries (TLICS). A total score > 5 indicates surgical management[8]

Category	Findings	Score
Radiological signs	Compression fracture Burst component Distraction trauma Translation or rotation	1 1 2 3
Neurological status	Intact Radicular injury Complete spinal cord injury Incomplete spinal cord injury Cauda equina syndrome	0 2 3 3 3
Posterior ligamentous complex integrity	Intact Indeterminate Proven injury	0 2 3
Predictors	Non-surgical Surgeon's decision Surgical	0-3 4 > 4

hours (preferably 24 hours) is beneficial. Although delaying fixation in patients with less severe injuries may be convenient for scheduling, it increases hospital resource utilization and patient complications[12-15].

The ASIA scale allows for more accurate predictions: patients with grade A have an 8.3% chance of walking independently 1 year after the injury, while those with grade D have a 97.3% chance[16].

Conclusions

High-dose IV steroids are ill-advised due to the increased risk of wound infection. It has been shown that early surgical management (< 24 hours) of SCI patients with instability and spinal cord injury, with progressive incomplete neurological deficit and spinal cord compression, requires urgent stabilization and decompression surgery.

Acknowledgments

The authors especially wish to acknowledge Dr. Miguel Ángel Ruiz Vaca, a brilliant neurosurgeon, and a mentor in the training of future physicians in neurosurgery. The authors consider themselves fortunate to have crossed paths during their academic journey.

Authors' contributions

C. Morales-Valencia: drafting, review, and editing. M.Á. Vaca-Ruiz: drafting, review, and editing. J.R. Solís-Pérez: review and editing. E. Morales-Valencia: review and editing; M.M. Escobar-Gasca: review and editing.

Funding

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

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

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables or their corresponding captions or legends.

References

1. Khurana B, Sheehan SE, Sodickson A, Bono CM, Harris MB. Traumatic thoracolumbar spine injuries: what the spine surgeon wants to know. Radiographics. 2013;33:2031-46.
2. Kumar R, Lim J, Mekary RA, Rattani A, Dewan MC, Sharif SY, et al. Traumatic spinal injury: global epidemiology and worldwide volume. World Neurosurg. 2018;113:e345-63.
3. Almendárez-Sánchez CA, Sotelo-Popoca T, Tafur-Grandett AA, Huato-Reyes R. Technical note: In Mexico, the majority of 147 traumatic spinal cord injuries occurred in the thoracic spine for young males. Surg Neurol Int. 2020;11:162.
4. Kumar S, Patralekh MK, Boruah T, Kareem SA, Kumar A, Kumar R. Thoracolumbar fracture dislocation (AO type C injury): A systematic review of surgical reduction techniques. J Clin Orthop Trauma. 2020; 11(5):730-741.
5. Rajasekaran S, Kanna RM, Shetty AP. Management of thoracolumbar spine trauma: An overview. Indian J Orthop. 2015;49(1):72-82
6. Abbasi Fard S, Skoch J, Avila MJ, Patel AS, Sattarov KV, Walter CM, et al. Instability in Thoracolumbar Trauma: Is a New Definition Warranted? Clin Spine Surg. 2017;30(8):E1046-E1049.
7. Khurjekar K, Kulkarni H, Kardile M. Treatment algorithm for unstable burst fractures. Int J Spine. 2016;1(2):27-32.
8. Vaccaro AR, Oner C, Kepler CK, Dvorak M, Schnake K, Bellabarba C, et al. AOSpine Spinal Cord Injury & Trauma Knowledge Forum. AOSpine thoracolumbar spine injury classification system: fracture description, neurological status, and key modifiers. Spine (Phila Pa 1976). 2013;38(23):2028-37.

9. Thomas AX, Riviello JJ Jr, Davila-Williams D. Pharmacologic and acute management of spinal cord injury in adults and children. Curr Treat Options Neurol. 2022;24:285-304.
10. Wardrope J, Ravichandran G, Locker T. Risk assessment for spinal injury after trauma. BMJ. 2004;328:721-3.
11. Holmes JF, Miller PQ, Panacek EA, Lin S, Horne NS, Mower WR. Epidemiology of thoracolumbar spine injury in blunt trauma. Acad Emerg Med. 2001;8:866-72.
12. Lindsey RW, Gugala Z, Pneumaticos SG. Injury to the vertebra and spinal cord. En: Moore EE, Feliciano DV, Mattox KL, editors. Trauma. 5th ed. New York: McGraw-Hill; 2004. p. 459-92.
13. Fehlings MG, Vaccaro A, Wilson JR, Singh A, W Cadotte D, Harrop JS, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One. 2012;7:e32037.
14. Piazza M, Schuster J. Timer of surgery after spinal cord injury. Neorosurg Clin North Am. 2017;28:31-9.
15. Croce MA, Bee TK, Pritchard E. Does optimal timing for spine fracture fixation exist? Ann Surg. 2001;233:851-8.
16. van Middendorp JJ, Goss B, Urquhart S, Atresh S, Williams RP, Schuetz M. Diagnosis and prognosis of traumatic spinal cord injury. Global Spine J. 2011;1:1-8.

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LETTER TO THE EDITOR

Putting meaning into words: primary progressive aphasia, a semiological approach

Más allá de las palabras: afasia primaria progresiva, un abordaje semiológico

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To the Editor,

In recent months, frontotemporal dementia and aphasias have gained relevance due to their appearance in public figures. Although these neurodegenerative disorders have well-defined diagnostic criteria, it is often difficult to use them practically because the terminology they use can be elaborate and sometimes confusing. To make matters worse, in the case of primary progressive aphasias (PPA)[1], there are elements that, due to the nature of our language, cannot be applied so easily. For this reason, we would like to present a simplified guide for examining language in people with suspected PPA.

Step 1: Spontaneous speech

This refers to speech that is expressed verbally without any written support. For diagnostic purposes of PPA, 4 important elements must be evaluated: speech, fluency, grammar, and word retrieval.

Speech apraxia is a characteristic element of the non-fluent variant of PPA (nfvPPA). To detect it, it is necessary to listen to the patient and their speech. Additionally, syllable repetition involving alternating mouth and tongue movements, such as the syllables/pa/-/ta/-/ka/-/da/, is widely used. The patient can also be asked to count from 1 to 20 as quickly as possible[2]. Grammatical changes and reduced fluency are other findings in nfvPPA.

Decreased word retrieval showing as a "tip of the tongue" phenomenon and pauses to "search" for words, is a classic element of the logopenic variant of PPA (lvPPA)[1].

Step 2: Repetition

Repetition consists in the oral reproduction of the information heard. For its evaluation, the patient can be asked to repeat words and phrases. A few examples can be found in various screening tests widely used in the clinic[3,4]. Difficulty in phrase repetition is a characteristic finding of lvPPA.

Step 3: Comprehension

To understand a message, we need proper processing of the speech sounds that make up words, their

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Date of reception: 20-05-2024
Date of acceptance: 13-06-2024
DOI: 10.24875/ANCE.M24000025

Available online: 14-11-2024
Arch Neurocien (Eng). 2024;29(3):115-118
www.archivosdeneurociencias.mx

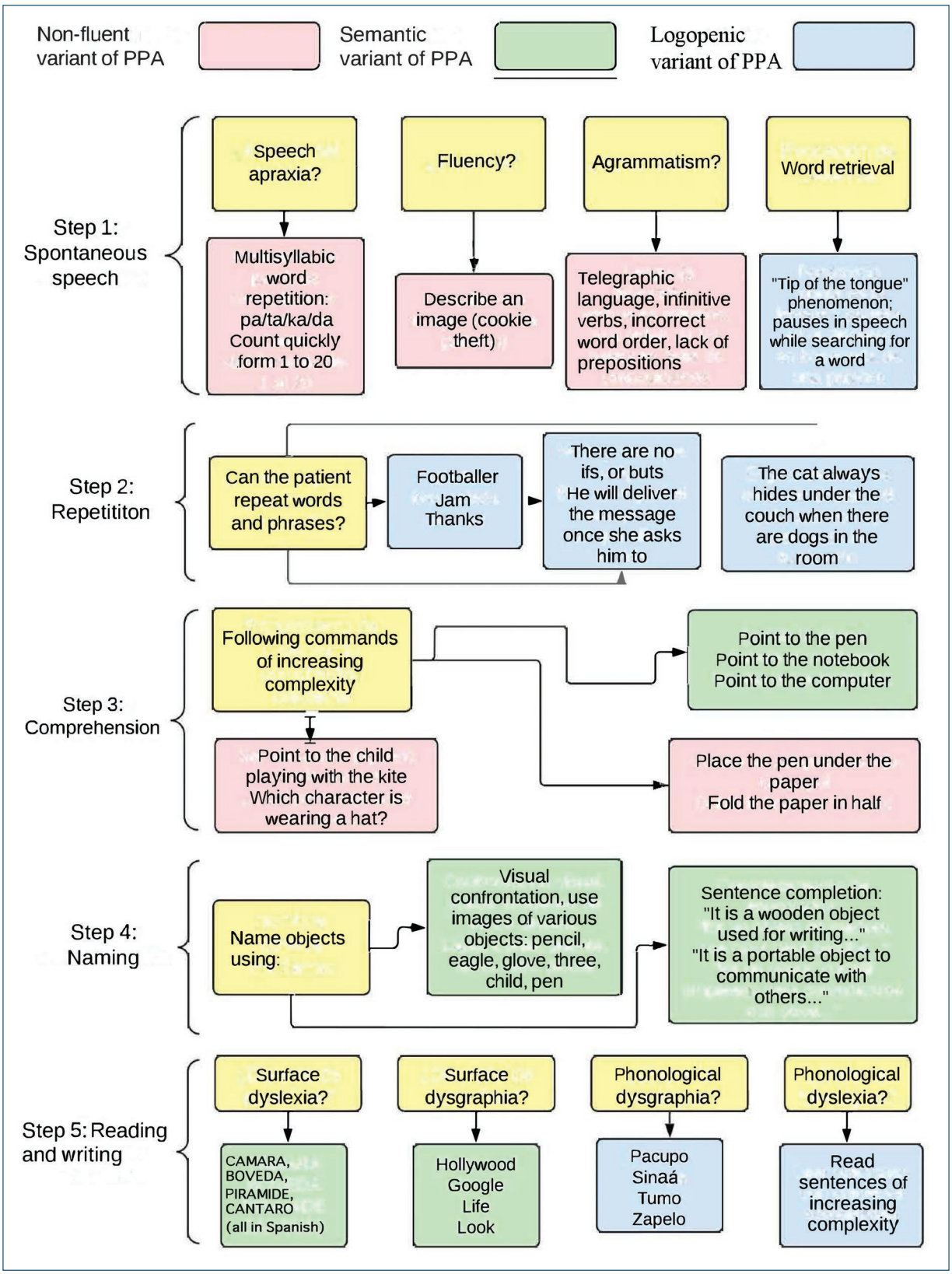

Figure 1. Algorithm for language assessment in patients with suspected primary progressive aphasia (PPA). Colors indicate the PPA subtype in which the deficit is most frequently found.

meanings, and the grammatical rules that allow their correct organization and linking. The evaluation starts with isolated words (e.g., "point to the pen") and then moves to executing commands with increasing complexity (e.g., "fold the paper in half")[5].

In patients with the semantic variant of PPA (svPPA), there is a severe deficit in word comprehension, while in patients with nfvPPA, the comprehension of complex commands is affected.

Step 4: Naming

Naming exploration should include images from different categories, starting with familiar and everyday objects (e.g., an image of a shoe) and progressing to less common objects (e.g., an image of an eagle or a koala, etc.). The patient may also be asked to name an object based on a verbal description provided by the examiner (e.g., "it is a wooden object with a graphite tip used for writing"). This method ensures that a visual processing deficit (visual agnosia) is not categorized as a language problem[6].

Anomia is one of the most significant features in svPPA and lvPPA. Patients with svPPA classically present semantic paraphasias, which can correspond to incorrect categorization (e.g., calling a lion a "dog" or a "goat"), or overgeneralization due to the gradual loss of specific lexical labels stored in semantic memory (e.g., calling a lion and a rhinoceros "animals"). Other errors include circumlocution responses (e.g., "it lives in the jungle…" when trying to name a lion). Anomia in lvPPA is usually considerably less severe than than in svPPA[6,7].

Step 5: Reading and writing

In patients with suspected PPA, the writing and reading disorders found are of the surface and phonological types. The former involves a change in the direct route consisting of reading the word based on its visual recognition (not letter-by-letter recognition); in the latter, the opposite occurs, with dysfunction in the indirect route involved in obtaining the meaning of the word letter by letter[8].

Phonological dysgraphia/alexia

These types of disorders are particularly observed in lvPPA and consist, respectively, in difficulty writing pseudowords and substituting words with others of similar sound when reading (e.g., "cara" instead of "casa"). Logatoms and pseudowords useful for detection include "*sinapa*," "*pacupo*," "*tumo*," "*capeto*," "*zapelo*," and "*basomedo*"[9].

Surface dysgraphia/dyslexia

These manifest through errors writing or pronouncing words whose written and spoken forms do not correspond precisely. This is much more evident in languages other than Spanish. In Spanish-speaking populations, patients may be asked to write words of foreign origin, such as "lady," "life," "Google," or "Hollywood." In cases of surface dyslexia, some authors suggest using cards with words written in capital letters and without accents (e.g., "*BOVEDA*" instead of "*bóveda*," "*CAMARA*" instead of "*cámara*," "*CANTARO*" instead of "*cántaro*," or "*PIRAMIDE*" instead of "*pirámide*"); if the patient can read the word correctly, it means that the direct route is preserved, and therefore there is no surface dyslexia[10].

Conclusions

The findings should be interpreted considering the specific age, education, and sociocultural level of each patient.

The tools described are not intended to replace a comprehensive neurological, cognitive, and neuropsychological evaluation; on the contrary, they aim to provide primary care physicians with the basic skills to assess, characterize, and categorize patients based on their clinical phenotype (Fig. 1). This is important because it has prognostic implications for the patients and their families, in addition to enabling appropriate rehabilitation strategies and early inclusion in clinical trials that could alter the course of the disease.

Authors' contributions

R. Medina-Rioja: conception, team organization, figure design, drafting, and manuscript review. S. Saldivar-Dávila: conception, drafting, and manuscript and figure review. C. Reyes-Méndez: drafting, manuscript and figure review. F. Charaf-Kapellmann: drafting and manuscript review. R. Ruiz-Garcia: drafting, manuscript and figure review.

References

1. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1006-14.

2. González-Victoriano R, Toledo-Rodríguez L. Apraxia del habla: evaluación y tratamiento. Revista Neuropsicología, Neuropsiquiatría y Neurociencias. 2015;15:141-58.
3. Reyes de Beaman S, Beaman PE, García-Peña C, Villa MA, Heres J, Córdova A, et al. Validation of a modified version of the Mini-Mental State Examination (MMSE) in Spanish. Aging, Neuropsychology, and Cognition. 2004;1:1-11.
4. MoCa Cognition. Available in: https://mocacognition.com
5. Richardson JD, Dalton SG. Assessment of language impairment and function. Handb Clin Neurol. 2022;185:175-93.
6. Rohrer JD, Knight WD, Warren JE, Fox NC, Rossor MN, Warren JD. Word-finding difficulty: a clinical analysis of the progressive aphasias. Brain. 2008;131:8-38.
7. Marshall CR, Hardy CJD, Volkmer A, Russell LL, Bond RL, Fletcher PD, et al. Primary progressive aphasia: a clinical approach. J Neurol. 2018; 265:1474-90.
8. Ardila-Ardila A. Neuropsicología del lenguaje. En: Tirapu-Ustárroz J, Ríos-Lago M, Maestú F, editors. Manual de neuropsicología. Barcelona: Viguera Editores; 2008. p. 99-122.
9. Peña Casanova J. Programa Integrado de Exploración Neuropsicológica (PIEN) - Test Barcelona. Barcelona, España: Masson; 1990.
10. Matías-Guiu JA, Cuetos F, Cabrera-Martín MN, Valles-Salgado M, Moreno-Ramos T, Carreras JL, et al. Reading difficulties in primary progressive aphasia in a regular language-speaking cohort of patients. Neuropsychologia. 2017;101:132-40.