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EDITORIAL

Advances in neuroscience from a Latin American perspective

Avances en neurociencia desde una perspectiva latinoamericana

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This issue of the Revista Mexicana de Neurociencia (RMN) brings together a compelling collection of articles that underscore both the scientific rigor and the clinical relevance of contemporary neuroscience research in Latin America. These contributions, emerging from diverse institutions and disciplines, reflect the growing commitment to evidence-based neurology and the exploration of innovative diagnostic and therapeutic frontiers. This issue spans neuro-oncology, neurovascular medicine, congenital neurovascular anomalies, and neurodegenerative disorders, offering a panoramic view of the challenges and progress in the field.

The first original article by Jimenez-Ruiz et al.[1], titled *"Epidemiology of pituitary tumors treated by Gamma Knife radiosurgery in Mexico: a single-center study,"* provides a detailed retrospective analysis of 111 patients with pituitary adenomas treated with Gamma Knife Radiosurgery (GKR) over 17 years. The authors report that GKR was effective in achieving radiographic improvement in nearly 40% of cases, particularly when tumors lacked chiasmatic extension and visual field abnormalities were absent before treatment. Importantly, the study documents a complete absence of acute or chronic complications, reinforcing the safety profile of GKR in experienced hands. This research not only fills an important epidemiological gap in the Mexican context but also underscores the relevance of radiosurgery as a valuable therapeutic adjunct in neuro-oncology. It contributes to the regional understanding of treatment patterns and clinical outcomes in pituitary tumors, an area that remains underrepresented in Latin American literature.

This article also reflects the importance of access to advanced technologies and the need for continued investment in radiosurgical infrastructure in middle-income countries. As radiosurgery becomes increasingly integrated into multidisciplinary neuro-oncology programs, studies such as this one demonstrate the feasibility and safety of implementation in Latin American settings. Furthermore, the findings advocate for the establishment of regional registries and collaborative databases to further assess long-term outcomes, cost-effectiveness, and patient quality of life.

In the domain of neurodegenerative disease, the review article by Murguiondo-Pérez et al.[2], *"Comprehensive approaches in Alzheimer's disease: From general aspects to stem cell therapy and antidiabetic use,"* offers a sweeping overview of the multifactorial pathophysiology of Alzheimer's disease (AD) and potential future treatments. The authors delve into the emerging relationship between insulin resistance and neurodegeneration, often referred to as "Type 3 Diabetes," and highlight how antidiabetic agents such as metformin and liraglutide may modulate this pathological axis. In addition, the article explores the therapeutic promise of neural stem cells, both in animal models and pre-clinical settings. This contribution is timely and critical, as it draws attention to the necessity of translational research in AD, a disorder with profound personal and societal impact.

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The article is particularly valuable for its holistic review of both established and experimental treatments, emphasizing the urgent need for Latin American countries to engage in early-phase clinical trials and collaborative studies. The potential repositioning of widely available pharmacologic agents such as antidiabetics presents an appealing and cost-effective research avenue, especially in health systems facing constrained resources. Furthermore, the discussion on stem cell therapies, while still in early development, encourages bioethical reflection and the establishment of national regulatory frameworks that foster responsible innovation.

The third article by Ortega-Moreno et al.[3], *"Etiological characterization of ischemic stroke in a neurovascular care unit in Mexico,"* analyzes 738 consecutive cases of ischemic stroke using the TOAST classification. Conducted in a well-structured neurovascular care unit, the study demonstrates how standardized etiological investigation can reduce the proportion of cryptogenic strokes and support individualized therapeutic decisions. Notably, the study reveals a higher prevalence of lacunar and atherothrombotic subtypes, contrasting with previously reported data from other Mexican centers, and suggesting the influence of setting, access to diagnostics, and patient demographics. This work exemplifies how structured clinical pathways and multidisciplinary evaluation can optimize outcomes in stroke medicine.

Stroke remains a leading cause of disability and death in Latin America, and this article contributes critical data to the understanding of stroke subtypes in Mexican populations. Moreover, the implementation of a dedicated stroke unit model serves as a reference for other institutions in the region. The emphasis on TOAST classification also underscores the importance of etiologic precision in selecting acute and secondary prevention strategies. Such approaches not only improve immediate care but have long-term implications for health planning and resource allocation.

The final article, *"Twig-like middle cerebral artery: pathophysiology and imaging approach,"* by Cox et al.[4], describes a rare congenital vascular anomaly that mimics moyamoya disease and presents diagnostic challenges. Through a retrospective angiographic review and two illustrative case reports, the authors emphasize the importance of precise imaging criteria in differentiating twig-like MCA from other steno-occlusive vasculopathies. Their analysis, supported by high-quality neuroimaging, contributes to a nuanced understanding of cerebrovascular malformations and underscores the role of advanced diagnostics in neurology.

By highlighting this rare entity, the article calls attention to the need for specialized neuroradiologic expertise and high-resolution imaging techniques in the evaluation of pediatric and young adult stroke. Given the rarity of the condition, this work advocates for the creation of clinical-imaging registries that can consolidate cases and inform future diagnostic criteria. In doing so, it bridges the gap between clinical observation and pathophysiological insight, and aligns with the RMN's commitment to advancing diagnostic excellence in neurology.

Taken together, the studies published in this issue of RMN provide a testament to the expanding breadth and depth of neurological research in Latin America. From radiosurgical interventions in pituitary tumors to cutting-edge perspectives on AD and stroke, as well as rare congenital anomalies, each article offers insights that are both locally relevant and globally resonant.

This collection highlights the importance of institutional collaboration, multidisciplinary integration, and methodological transparency. It affirms the need for continued investment in research infrastructure and training, as well as the value of publishing platforms that amplify Latin American neuroscience on the international stage. As neurology continues to evolve in complexity and scope, initiatives such as RMN remain essential for fostering dialog, disseminating knowledge, and guiding evidence-based clinical practice.

We commend the authors for their rigorous contributions and the editorial team for curating a robust and visionary issue.

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ORIGINAL ARTICLE

Epidemiology of pituitary tumors treated by gamma knife radiosurgery in Mexico: a single-center study

Amado Jimenez-Ruiz[1], Miguel García-Grimshaw[2], Lorena Valerdi-Contreras[3], Israel Anaya-Silva[3], Abel Cuevas-Solórzano[4], Alejandro Gutiérrez-Castillo[5], Cristina Torres-Mora[3], and José L. Ruiz-Sandoval[1]*

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Abstract

Objective: *Pituitary adenomas (PAs) represent the second most common intracranial tumors usually treated with surgery. Total resection is rare, so adjuvant radiosurgery is often indicated to control tumor growth. This study aims to describe a cohort of Mexican patients treated with Gamma Knife Radiosurgery (GKR) for PA over 17 years in a single center.* **Methods:** *The records of adult patients treated with GKR for PA at San Javier Hospital in Guadalajara, Mexico, from 1998 to 2015 were retrospectively reviewed. The analyzed factors included tumor imaging characteristics, visual field abnormalities, prior treatment, and radiographical improvement after radiosurgery.* **Results***: This study included 111 patients (70 females, median age 39.5 years, [IQR: 33-51]). The median tumor volume was 3.55 cm^3 (2.14-6.82), and the median diameter was 0.95 mm (0.5-1.4). We found an abnormal visual field pre-GKR in 33 (29%) patients. The most common type of tumor was prolactinoma (43%). The median dose of radiation was 21 Grays (16-25). Forty-five (39.5%) patients had radiographic improvement. The variables associated with significant radiographic improvement were having a normal pre-treatment visual field campimetry (p = 0.03; odds ratio [OR] = 2.4 [95% confidence interval (CI), 1.05-5.48]) and the absence of chiasmatic extension (p = 0.03; OR = 2.66 [95% CI, 1.06-6.99]) which are essential to anticipate and improve outcomes in patients with pituitary tumors.* **Conclusions***: GKR was safe and valuable for the volumetric control of PA. Nearly half the patients had radiographic improvement without reported adverse effects (different from hormonal deficiencies) within a median follow-up of 12 months.*

Keywords: *Gamma knife radiosurgery. Radiosurgery. Pituitary neoplasms. Pituitary adenoma.*

Epidemiología de los tumores hipofisarios tratados con radiocirugía con bisturí gamma en México: un estudio de un solo centro

Resumen

Objetivo: *Los adenomas pituitarios representan el segundo tumor intracraneal más frecuente y usualmente son tratados mediante cirugía y radiocirugía. El objetivo de esta cohorte es describir el uso de radiocirugía con bisturí de rayos gamma en México.* **Métodos:** *Se realizó una revisión retrospectiva de pacientes tratados mediante radiocirugía con bisturí de rayos gamma en el Hospital San Javier en Guadalajara, México de 1998 al 2015. Las variantes analizadas incluían las características imagenológicas del tumor, las anormalidades del campo visual previo al tratamiento y la mejoría radiográfica posterior a la radiocirugía.*

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Resultados: *En total 111 pacientes fueron incluidos (70 mujeres, edad media 39.5 años [IQR: 33-51]) en este estudio. El volumen promedio del tumor fue 3.55 cm^3 (2.14-6.82) y el diámetro de 0.95 mm (0.5-1.4). Encontramos alteraciones del campo visual previo a la radiocirugía en 33 pacientes (29%). La dosis promedio de radiación fue 21 Gy (16-25). Se observó una mejoría radiológica en 55 pacientes (39.5%); las variables asociadas con esta mejoría fueron un campo visual por campimetría normal previo al procedimiento (p = 0.03; OR 2.4 [95% CI, 1.05-5.48]) y la ausencia de extensión tumoral al quiasma óptico (p = 0.03; OR 2.66 [95% CI, 1.06-6.99]); los cuáles son esenciales para anticipar y mejorar los resultados a futuro con este tipo de ciurgía.* **Conclusiones:** *La radiocirugía con bisturí de rayos gamma fue segura y demostró utilidad en el control volumétrico de adenomas pituitarios. El 39.5% de los pacientes obtuvieron una mejoría radiológica sin reporte de efectos adversos, diferentes a deficiencias hormonales, en un seguimiento a 12 meses.*

Palabras clave: *Radiocirugía con bisturí de rayos gamma. Radiocirugía. Adenoma pituitario. Prolactinoma.*

Introduction

Pituitary tumors are categorized based on their size and endocrine function. The treatment of these tumors aims to control tumor growth and normalize hormone levels[1,2], utilizing various therapeutic approaches such as medication, surgery, and radiotherapy. Surgical resection is typically the initial management strategy for these tumors, except in specific instances where medical therapy, such as for prolactinomas (PRLs), is preferred. However, achieving total resection can be challenging, particularly in tumors that invade the cavernous sinus[3]. In such cases, adjuvant radiation therapy, with or without radiosurgery, has demonstrated excellent results in preventing post-surgical tumor growth while minimizing adverse effects[4]. A range of factors, including tumor volume, histology, previous use of radiation, proximity to optic nerves, and the preservation of endocrinological function, determines the prescribed radiation dose. The mortality rate associated with these tumors is low, but the morbidity related to surrounding structures in the sellar region can be significant[5,6].

Medical professionals increasingly recognize Gamma Knife Radiosurgery (GKR) as an adjunct treatment for recurrent or residual disease, particularly in lesions that invade parasellar structures. Although complications following GKR are rare, chronic issues can arise, including cranial neuropathies (such as optic neuritis), panhypopituitarism, secondary neoplasms, stroke, and radionecrosis. Acute complications are infrequent, but symptoms such as headache, dizziness, seizures, syncope, optic neuritis, and localized infection may occur at the site where stereotactic frame posts were inserted[7-9]. GKR has long been used in Mexico to treat patients with pituitary adenomas (PA); however, there is no epidemiological information or clinical results. This study aims to describe a cohort of patients with pituitary tumors treated with GKR, a topic that has yet to be explored in our country.

Material and methods

In this retrospective study, we collected information from adult patients (≥ 18 years) treated with GKR for pituitary tumors at Hospital San Javier in Guadalajara, Mexico, from 1998 to 2015. Table 1 summarizes the patient's characteristics and prognosis factors associated with radiographical improvement. We extracted data from medical records, which included tumor imaging characteristics (such as size), endocrine function, visual field abnormalities, previous medical or surgical treatments, and radiographic outcomes following GKR. Cases with incomplete data and those with an alternative histopathological diagnosis were excluded from the study.

Radiographic improvement was defined as a reduction in tumor size of at least 1 mm, as detected by contrast-enhanced magnetic resonance imaging (MRI), utilizing 1-2 mm slices with a focus on the sellar region during any point in the follow-up period. We defined abnormal visual field campimetry as any irregularity observed through digital campimetry that could be attributed to the compression of the optical nerves caused by a pituitary tumor. The total radiation dose administered to each tumor was recorded in Grays (Gy). Prior medical treatments consisted of bromocriptine, cabergoline, octreotide, ketoconazole, or pegvisomant, each given for a minimum of 3 months before the radiosurgery – any surgical intervention before GKR, whether transsphenoidal or transcranial, was classified as prior surgery. Following a surgical procedure, partial resection was defined as any indication of residual disease observed through contrast-enhanced MRI of the sellar region.

Differences between categorical variables were analyzed using the χ^2 test, while differences in continuous variables were evaluated using the Mann-Whitney U test. A $p < 0.05$ was considered statistically significant. IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA), was used for statistical analysis. The Local Ethical Committee approved this study.

Table 1. Population and tumor baseline characteristics

Variables	Total
Sex (%) Female Male	 70 (64) 41 (36)
Age (years)	39.5 (33-51)
Abnormal visual field test by campimetry	33 (29%)
Tumor radiographical features Volume (cm^3) Diameter (cm) Chiasmatic extension Cavernous sinus extension	 3.55 (2.14-6.82) 0.95 (0.5-1.4) 24 (21.1%) 30 (26.3%)
Previous treatment (%) Previous medical treatment Previous surgery	 63 (55.3) 60 (52.6)

Results

We analyzed 135 medical records, with 24 cases excluded for specific reasons: 10 patients were diagnosed with craniopharyngioma, and 14 were pediatric cases. This resulted in a final cohort of 111 patients, of which 70 (64%) were female, with a median age of 39.5 years (33-51). Thirty-three patients (29%) presented abnormal visual field campimetry. The median tumor volume was 3.55 cm^3 (2.14-6.82), with a median diameter of 0.95 cm (0.5-1.4). Among the 111 patients, 63 (55.3%) had received medical treatment before GKR, 60 (52.6%) had undergone previous surgical interventions, and 51 (47.4%) had not. (Table 1) The most frequently identified tumor type was PRL, present in 48 cases (43.2%), followed by growth hormone (GH) producing tumors in 18 cases (16.2%), and adrenocorticotropic hormone (ACTH) producing tumors in 8 cases (7.2%). In addition, there were three cases (2.7%) of mixed co-producing tumors and 37 (33.3%) non-functional tumors (Fig. 1).

The median administered radiation dose was 21 (16-25) Gy, and it was determined by various factors, mainly tumor volume, histology, previous radiation, and endocrine function. Radiographic improvement following GKR was observed in 45 patients (39.5%). Throughout the follow-up period, which had a median duration of 12 months (range 8-36), no acute or chronic complications were reported, including cranial neuropathies, optic neuritis, hypopituitarism, cerebrovascular events, secondary neoplasms, or cognitive disorders. Two significant variables were identified as being associated with improved radiographic outcomes post-GKR: patients who exhibited a normal pre-treatment visual field campimetry were more likely to experience favorable results (p = 0.03; odds ratio [OR] = 2.4 [95% confidence interval (CI), 1.05-5.48]), as were those without chiasmatic extension (p = 0.03; OR = 2.66 [95% CI, 1.06-6.99]) (Table 2). No significant relationship was found between the radiation dose (p = 0.40) or tumor type and the degree of radiographic improvement (Fig. 2).

Table 2. Variables associated with radiographical improvement

Variable	Odds ratio	95% confidence interval	p
Normal visual field test	2.4	1.05-5.48	0.03
Non-chiasmatic involvement	2.66	1.06-6.69	0.03
Non-cavernous sinus involvement	1.8	0.77-4.18	0.17
Previous medical treatment	1.01	0.47-2.17	0.95
Previous surgery	1.9	0.88-4.09	0.09

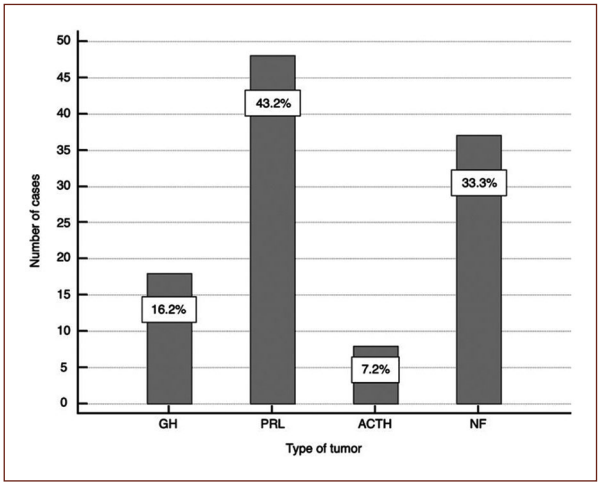

Figure 1. Frequency of tumor subtype. GH: growth hormone; PRL: prolactin; ACTH: adrenocorticotropic hormone; NF: non-functioning.

Discussion

The prevalence of pituitary tumors within our study population is consistent with findings documented in the literature by researchers worldwide[10-19]. Prolactinoma was identified as the predominant subtype, followed by non-functioning adenomas, GH-producing

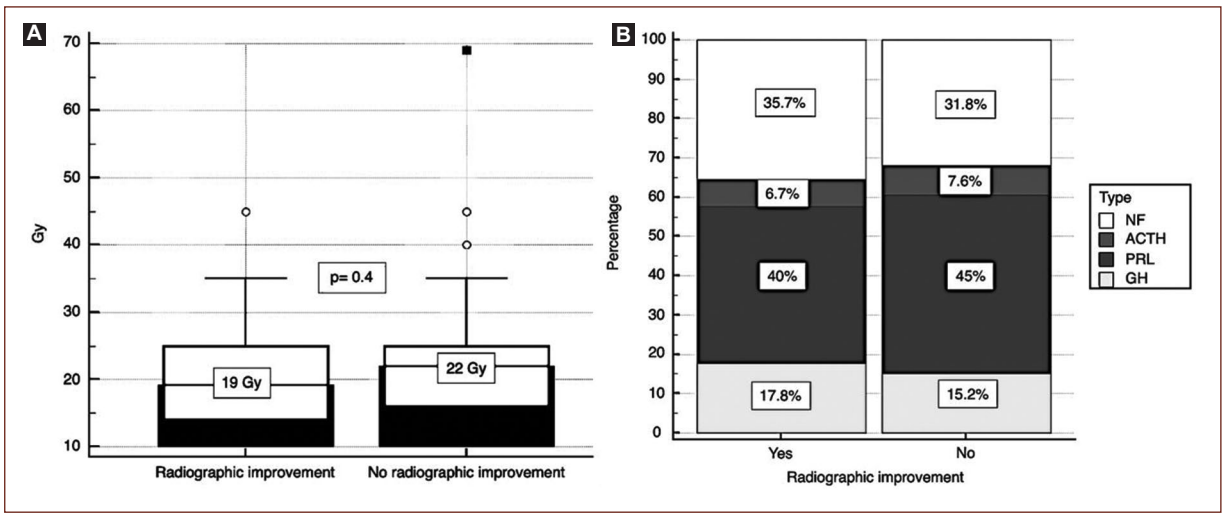

Figure 2. Radiographic improvement after GKR according to radiation dose and tumor type. **A:** patients who did not have radiographic improvement received more radiation than those with radiographic improvement, but the difference was not significant (p = 0.40). **B:** there were no statistically significant differences regarding the type of tumor and its association with radiographic improvement, meaning that no tumor by itself was more associated with presenting radiographic improvement with GK treatment. GH: growth hormone; PRL: prolactin; ACTH: adrenocorticotropic hormone; NF: non-functioning.

tumors, and ACTH-producing tumors. Notably, no cases of thyroid-stimulating hormone-producing tumors were observed. In addition, we recorded three cases of mixed co-producing tumors (GH and PRL), one of which was confirmed through positive immunobiological markers and the other by elevated serum hormone levels.

This study determined that the absence of extension to the optic chiasma and a normal pre-treatment visual field campimetry were significant factors associated with radiographic improvement following GKR. These results align with observations reported in other studies[10-19]. We documented no adverse effects related to GKR during the median follow-up duration of 12 months, demonstrating the safety of this procedure and paving the way for establishing its conventional use in this type of tumor. Tumors subjected to prior surgical resection demonstrated a requirement for a lower radiation dose, indicating a tendency for radiographic improvement in long-term follow-up, supporting the theory that GKR should be used as an adjuvant to conventional neurosurgery.

We also noted that the type of tumor did not exhibit a significant correlation with radiographic improvement post-GKR. The results suggest that radiosurgery is effective and safe for patients with residual or recurrent disease, with nearly half of the tumors demonstrating radiographic improvement and no complications. This study did not include information regarding hormonal deficiencies due to a lack of records.

Conclusion

The management of pituitary tumors has advanced significantly in recent years and should include a comprehensive team of neurosurgeons, endocrinologists, and radio oncologists. At present, transsphenoidal surgery appears to be the treatment of choice in patients with low surgical risk, mainly when the tumor produces a mass effect on the optical system, or there is hormone overproduction. However, approximately 20-50% of patients may experience recurrent or residual disease, particularly when the tumors invade difficult-to-reach areas like the cavernous sinus. GKR can be pivotal in such cases[15]. The limitations of our study include its retrospective nature, where data obtained from medical records may be biased due to medical record accuracy. Furthermore, since hormone levels before and after GKR were not systematically available, no conclusions can be made about the biochemical effect of GKR in these tumors, which is as essential as volumetric control.

In this study, GKR was safe and beneficial for the volumetric control of PAs. Nearly half of our patients had radiographic improvement without any report of adverse effects (unrelated to hormonal deficiencies)

associated with treatment within a median follow-up period of 12 months. Positive prognosis factors associated with radiographical improvement include a normal pre-treatment campimetry and the absence of a tumor affecting the optic chiasm. More research is needed in our country to replicate these findings in other centers.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

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

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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ORIGINAL ARTICLE

Etiological characterization of ischemic stroke in a neurovascular care unit in Mexico

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Abstract

Objective: *This study aimed to elucidate the diagnostic experience of our neurovascular care unit (NCU) in managing consecutive cases of cerebral infarction, detailing the prevalence of etiologies using the Trial of Org 10172 in acute stroke registry (TOAST) classification and comparing it with prior Mexican studies.* **Methods:** *A descriptive study of consecutive cases was conducted on patients diagnosed with ischemic stroke hospitalized in our NCU from September 2019 to July 2022. Patients underwent standardized diagnostic assessments by internists and neurologists, including neuroimaging (computed tomography [CT] and/or magnetic resonance imaging of the brain) and complementary studies (carotid Doppler ultrasound, 24-h Holter monitoring, echocardiogram). All patients had TOAST etiological classification, National Institute of Health Stroke Scale, and modified Rankin Scale evaluations.* **Results:** *A total of 738 subjects (57% male and mean age of 61 years) were included. Hypertension (61%), diabetes (49%), and dyslipidemia (11%) were common risk factors. Neuroimaging was performed on 95.7% of patients, with CT being the most prevalent (72.8%). The TOAST classification revealed 31.3% atherothrombotic, 24.7% lacunar, 15.4% cardioembolic, and 25.5% cryptogenic cases.* **Conclusions:** *The establishment of NCUs enhances ischemic stroke management, improving patient outcomes and reducing recurrence. Until stroke units become widespread, a structured evaluation by trained specialist physicians remains essential.*

Keywords: *Stroke. Etiology. Neurovascular care unit.*

Caracterización etiológica del ictus isquémico en una unidad de cuidados neurovasculares en México

Resumen

Objetivo: *Este estudio tuvo como objetivo detallar la experiencia diagnóstica de nuestra Unidad de Cuidados Neurovasculares (UCN) en el manejo de casos consecutivos de ictus isquémico, detallando la prevalencia de etiologías utilizando la clasificación TOAST y comparándola con estudios previos en México.* **Métodos:** *Se realizó un estudio descriptivo de casos consecutivos en pacientes diagnosticados con ictus isquémico-hospitalizados en nuestra Unidad de Cuidados Neurovasculares desde septiembre de 2019 hasta julio de 2022. Los pacientes fueron sometidos a evaluaciones diagnósticas*

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estandarizadas por internistas y neurólogos, que incluyeron neuroimagen (TC y/o RMN cerebral) y estudios complementarios (ultrasonido Doppler carotídeo, monitoreo Holter de 24 horas, ecocardiograma). Todos los pacientes tuvieron clasificación etiológica TOAST, evaluaciones NIHSS y escala modificada de Rankin. **Resultados:** *Se incluyeron un total de 738 sujetos (57% hombres, edad media 61 años). La hipertensión arterial (61%), la diabetes (49%) y la dislipidemia (11%) fueron factores de riesgo comunes. Se realizó neuroimagen en el 95.7% de los pacientes, siendo la TC la más prevalente (72.8%). La clasificación TOAST reveló casos aterotrombóticos (31.3%), lacunares (24.7%), cardioembólicos (15.4%) y criptogénicos (25.5%).* **Conclusiones:** *Un enfoque sistemático en la evaluación del ictus isquémico puede mejorar los resultados del paciente y reducir los riesgos de recurrencia, subrayando el papel fundamental de los médicos especialistas en el manejo del ictus isquémico dentro del sector de la salud pública.*

Palabras clave: *Ictus isquémico. Etiología. Unidad de Cuidados Neurovasculares.*

Introduction

Ischemic stroke is one of the leading causes of death and disability worldwide[1], as well as a major cause of hospitalization in neurology services. In 2019, the incidence of ischemic stroke in Mexico was 58.6/100,000 inhabitants, occurring in men in 56.5% of cases[2]. Ischemic stroke represents a significant public health issue globally, resulting in substantial clinical impairment in patients, associated residual disability, decreased work capacity, and socioeconomic burden on families[3].

The etiological classification of ischemic stroke is a contentious issue in Mexico due to limited availability for patient evaluation, including laboratory and imaging studies. It is common for adjunct studies such as Doppler ultrasound of neck vessels, echocardiography, and imaging of intracranial arteries with magnetic resonance angiography or computed tomography (CT) angiography to be deferred to subsequent visits, leading to a higher percentage of cases with undetermined etiology.

Current guidelines for the management of acute cerebral infarction consider complementary studies essential for achieving accurate etiological definition and, consequently, better patient care. This becomes feasible with the presence of neurovascular care units (NCUs) or stroke units[4] and the standardization of quality indicators, including complementary studies and therapeutic response times, thus improving patients' functional status at discharge, preventing intrahospital complications, and stroke recurrence[5-7].

The primary objective of this study was to detail the experience of our NCU in the standardized diagnostic approach of consecutive cerebral infarction patients, describing the prevalence of etiologies according to the Trial of Org 10172 in Acute Stroke Registry (TOAST) classification[8] and comparing it with previous publications in Mexico.

Materials and methods

A descriptive study of consecutive cases was conducted, including patients diagnosed with ischemic stroke registered in the i-Registro-Neurovascular database of the Neurology Service at the "Dr. José Eleuterio González" University Hospital and hospitalized in our NCU between September 2019 and July 2022.

All included patients underwent standardized diagnostic evaluation by internists and neurologists, which consisted of an initial neuroimaging study (CT and/or magnetic resonance imaging [MRI] of the brain), as well as complementary studies for the etiological determination of cerebral infarction, including carotid Doppler ultrasound, 24-h Holter monitoring, and transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE). All included patients underwent ischemic stroke classification according to the TOAST criteria[8,9]. Stroke etiology was determined as positive when classified as either probable–indicating strong clinical, imaging, and ancillary test support for a specific cause with most alternative etiologies excluded–or possible, where the available evidence suggested a particular cause, though further investigations might be required for definitive confirmation. If neither classification could be assigned with confidence, the stroke was designated as cryptogenic. This approach adhered to the original TOAST criteria established by Adams et al. In addition, the National Institute of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) were used for patient evaluation during their hospital stay.

Comorbidity was defined for patients who: (1) were known to have the disease, (2) had a personal history of the disease, or (3) were under treatment with medications. A sedentary lifestyle was defined as not engaging in physical activity beyond daily activities. Young stroke was defined for patients who had ischemic stroke before the age of 55[10].

Categorical variables were reported as frequencies and percentages, whereas numerical variables were reported as measures of central tendency and dispersion. IBM SPSS Statistics version 25 was used for statistical analysis.

Results

A total of 738 subjects were included (57% male), with a mean age of 61 years (SD 14). The most prevalent risk factors within our sample were arterial hypertension (61%), diabetes mellitus (49%), and dyslipidemia (11%). 31% (n = 229) of cerebral infarctions occurred in patients under 55 years old. The average length of hospital stay was 8.66 days (SD 6.34). Upon admission, the mean NIHSS score was 8.07 points (SD 5.94). Regarding complications, 2.8% (n = 21) of patients suffered from cerebral hemorrhage/hemorrhagic transformation, and 1.5% (n = 11) suffered from a recurrent cerebral infarction. A complete description of patient characteristics is found in table 1.

The neuroimaging evaluation was performed on 95.7% of patients during hospital admission for suspected ischemic stroke, with non-contrast CT being the most frequently used, performed in 72.8% of cases. Subsequently, during hospitalization, complementary studies performed were: (1) angiotomography, magnetic resonance angiography, or transcranial Doppler in 95.3% of patients, for evaluation of intracranial vasculature; (2) Holter monitoring for at least 24 h in 64% of patients (although 92% had telemetry in their first 24 h of hospitalization); (3) TTE or TEE in 97.6% of patients; (4) Doppler ultrasound of the extracranial carotid and vertebral arteries in 92.7% of patients. A complete description of the imaging evaluation of patients is found in table 2.

Regarding etiological classification by TOAST within our sample, following interpretation of clinical and paraclinical studies, 31.3% (n = 231) corresponded to atherothrombotic origin, 24.7% (n = 182) lacunar, 15.4% (n = 114) cardioembolic, and 3.1% (n = 23) of other determined etiology. Despite the clinical and paraclinical methodology used for patient evaluation, 25.5% (n = 188) were finally classified as having undetermined or cryptogenic etiology.

Among evaluated patients who experienced a cerebral infarction before the age of 55, 62.4% (n = 143) were male, and 14.4% (n = 33) had a history of previous cerebral infarction. Regarding the etiological origin of ischemic stroke, it was found that 24.5% (n = 56) were of atherothrombotic origin, 32.3% (n = 74) lacunar, 10.5% (n = 24) cardioembolic, 3.9% (n = 9) of other determined etiology, and 28.8% (n = 66) cryptogenic. At hospital discharge, 50% (n = 94) of this subgroup of patients had a score of 0-2 on the mRS. Complications included 3.1% (n = 7) suffering from cerebral hemorrhage/hemorrhagic transformation.

Table 1. Population characteristics

Baseline characteristics	Total population (n = 738)
Sex (males), n (%)	419 (56.8)
Age (mean, SD)	61.17 (14)
Personal history, n (%)	
Diabetes mellitus	363 (49.2)
Hypertension	450 (61)
Dyslipidemia	84 (11.4)
TIA	29 (3.9)
Smoking	311 (42.1)
Alcoholism	338 (45.8)
Substance abuse	42 (5.7)
Sedentary lifestyle	510 (69.1)
Admission assessment	
NIHSS (mean, SD)	8.07 (5.94)
mRankin, n (%)	
0-2	273 (37.0)
3-5	444 (60.2)
TOAST, n (%)	
Atherothrombotic	231 (31.3)
Lacunar	182 (24.7)
Cardioembolic	114 (15.4)
Other determined cause	23 (3.1)
Cryptogenic	188 (25.5)
Complications, n (%)	
Cardiovascular	4 (0.5)
Cerebral hemorrhage/Hemorrhagic transformation	21 (2.8)
Recurrent cerebral infarction	11 (1.5)
Urinary tract infections	7 (0.9)
Kidney failure	4 (0.5)
Pneumonia	14 (1.9)
Discharge evaluation	
NIHSS (mean, SD)	5.68 (5.77)
mRankin, n (%)	
0-2	384 (52.0)
3-5	312 (42.3)
Length of hospital stay (mean, SD)	8.66 (6.34)
In-hospital mortality, n (%)	20 (2.7)

TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale; TOAST: trial of org 10172 in acute stroke treatment; SD: standard deviation.

Discussion

Ischemic stroke remains one of the leading causes of morbidity and mortality globally. Its multifactorial

Table 2. Diagnostic imaging

Diagnostic imaging studies, n (%)	Total population (n = 738)
Simple computed tomography	537 (72.8)
Simple magnetic resonance imaging	567 (76.8)
Computed tomography or magnetic resonance imaging	706 (95.7)
Computed tomography and magnetic resonance imaging	398 (53.9)
Angiotomography, magnetic resonance angiography, or transcranial Doppler	703 (95.3)
Carotid and vertebral Doppler ultrasound	684 (92.7)
24-h Holter monitor	471 (63.8)
Transthoracic echocardiogram (TTE)	535 (72.4)
Transesophageal echocardiogram (TEE)	25 (3.4)
Echocardiogram (ETT o ETE)	721 (97.6)

nature demands both precise diagnosis and personalized treatment. In this context, specialist physicians and neurologists play a crucial role in the initial evaluation, identification of underlying causes, and final diagnosis of ischemic stroke, as well as in identifying factors contributing to the recurrence of this disease. Standardized evaluation is essential for minimizing resulting brain damage and optimizing patient prognosis[11].

The etiological epidemiology of ischemic stroke in Mexico, as in other countries with economic health limitations, remains a poorly studied topic, with variable results according to available documented information[2,12]. Within the RENAMEVASC study, the cardioembolic subtype (24.7%) was designated as the most frequent etiological cause of ischemic stroke in Mexico, followed by lacunar (19.4%) and atherothrombotic (14.7%) subtypes. However, the classification of "Undetermined" as the ultimate cause of ischemic stroke corresponded to 36.6%, being the most frequent[13]. Similarly, in the subset of the PREMIER database, the most frequent etiological causes of ischemic stroke were cardioembolic (22%), lacunar (19%), and atherothrombotic (8%) subtypes. However, the "Cryptogenic" classification was also assigned a percentage of 42%[14].

It is interesting to evaluate, within this subset, the analyzed data and the proportionality of the etiological causes of ischemic stroke in patients evaluated within public medical centers compared to private centers. In public medical centers, a proportion of cryptogenic ischemic stroke cases of 45% was reported, whereas in private centers, it was 28%, generating a reduction of 17%. In public centers, the main imaging study performed for the evaluation of patients with ischemic stroke corresponded to CT of the skull, whereas in private centers, it was MRI of the skull, together with transcranial and carotid Doppler ultrasound, angiography, and echocardiogram[14].

On the other hand, Arauz et al. documented in the registry of the National Institute of Neurology and Neurosurgery that atherothrombotic was the most frequent etiological cause (25.1%), followed by cardioembolic and other determined etiology, with 24.5% and 17%, respectively. Truly cryptogenic etiology was documented in 6.4% of cases, and indeterminate cause with incomplete evaluation was documented in 11.2%. It is important to note that within their evaluation, 94.3% of patients underwent CT scans during their initial assessment, of which 71.77% underwent MRI after their initial assessment. Vascular evaluation was performed using cervical US in 50.4%, angio CT in 11.4%, and angio MRI in 18.3%. 34.5% underwent TTE as part of their evaluation. In addition, 12.9% of cases were evaluated using serum prothrombotic proteins[15]. A detailed comparison of etiological causes of acute ischemic stroke across different Mexican cohorts is presented in table 3.

A thorough evaluation of cardiovascular risk factors is imperative to understand the etiology of ischemic stroke. Specialist physicians should conduct meticulous analyses of patients to detect comorbidities that could contribute to the development of this pathology[16]. Internists play a fundamental role in managing these conditions, which may require anticoagulant therapy, antiplatelet medications, or surgical interventions[17]. Furthermore, close collaboration among specialist physicians, such as internists, neurologists, cardiologists, and vascular surgeons, is essential to accurately determine the etiological cause of stroke, facilitating the provision of comprehensive care for ischemic stroke through a more complete evaluation and additional therapeutic plans[18].

In situations where conventional risk factors do not fully explain the etiology of ischemic stroke, especially in patients < 55 years old, it is necessary to conduct a comprehensive investigation focused on possible underlying vasculopathy or coagulopathies, using specialized tests such as vascular imaging and thrombophilia panels, to identify less common but equally relevant

Table 3. Etiological characterization

Stroke etiology by TOAST classification	iReNe 2022 (%)	PREMIER 2018[§] (%)	PREMIER 2018	RENAMEVASC 2011 (%)	Arauz, et al. 2018 (%)
Atherothrombotic	31.3	8	17	14.7	25.1
Lacunar	24.7	19	16	19.4	15.1
Cardioembolic	15.4	22	20	24.7	24.5
Other determined etiology	3.1	5	9	4.6	17
Cryptogenic	25.5	42	28	36.6	6.4
Mixed	NR	5	9	NR	NR

Etiological classification by TOAST in various studies.
[§]Data obtained from the general population. Data was obtained from private hospitals.
NR: not reported.

causes of ischemic stroke[18]. By closely evaluating these risk factors and defining the etiology of ischemic stroke in patients, internists can take preventive measures to reduce the likelihood of occurrence or recurrence of a stroke[19]. In addition, routine health screening with prothrombotic screening coverage in patients under 55 years of age may help improve the determination of the cause of heart attack.

Recognizing and classifying the etiology of ischemic stroke, especially in populations with a high prevalence of cardiovascular risk factors, is essential for effective management of secondary prevention, improving short and long-term functional outcomes, reducing the burden of disability, improving quality of life, and reducing mortality related to this disease.

Conclusion

The establishment of NCUs enhances the initial evaluation, management, monitoring, and secondary prevention of patients with acute ischemic strokes. In the public health-care sector of our country, specialist physicians play a critical role in diagnosis, management, and risk factor identification, ensuring timely and accurate care, particularly in the absence of stroke units outside major urban centers. Until the widespread implementation of dedicated stroke units becomes feasible, adopting a standardized approach to ischemic stroke evaluation could substantially improve functional outcomes and reduce recurrence rates.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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

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ORIGINAL ARTICLE

Twig-like middle cerebral artery – pathophysiology and imaging approach

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Abstract

Objective: *A twig-like middle cerebral artery is an infrequent congenital disturbance that is difficult to distinguish from moyamoya disease. Cerebral angiography is essential for the differential diagnosis of stenotic-occlusive vasculopathies involving the middle cerebral artery.* **Methods:** *We explored the prevalence of the twig-like middle cerebral artery in our institution's angiography unit and reviewed the literature to clarify the imaging criteria.* **Results:** *The prevalence calculated in our anonymous database was 0.21%, which is in the frequency range described in the literature. Two cases that meet the diagnostic criteria and differ in clinical imaging characteristics are described in detail.* **Conclusions:** *Adequate imaging description allows precise diagnosis and approximation of the underlying etiopathogenic mechanism.*

Keywords: *Middle cerebral artery anomaly. Middle cerebral artery. Twig-like middle cerebral artery.*

Arteria cerebral media con variante tipo "rete" – fisiopatología y enfrentamiento imagenológico

Resumen

Objetivo: *La arteria cerebral media tipo "twig" o "rete" es una anomalía congénita infrecuente que es dificil de distinguir de la enfermedad de moyamoya. La angiografía cerebral es esencial para realizar el diagnóstico diferencial dentro de las vasculopatías esteno-oclusivas de arteria cerebral media.* **Métodos:** *Nosotros exploramos la prevalencia en nuestra base de datos anonimizada entre un total de 1428 angiografías diagnósticas realizadas entre enero del año 2010 y diciembre del 2023* **Resultados:** *La prevalencia resultó del 0.21%, lo cual está dentro del rango de lo reportado por la literatura internacional. Reportamos de forma detallada dos casos que reunen los criterios con diferencias clínicas-imagenológicas entre ellos.* **Conclusiones:** *La adecuada descripción imagenológica permite realizar un diagnóstico preciso y a través de la angio-arquitectura aproximarse al mecanismo etiopatogénico subyacente.*

Palabras clave: *Anomalía en arteria cerebral media. Arteria cerebral media tipo rete. Vasculopatía congénita.*

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Introduction

Twig-like middle cerebral artery (MCA) is a rare vascular anomaly in which a plexiform network of small vessels is seen to replace the M1 segment of the MCA[1]. The prevalence in the Latin American population has been described as around 0.088%[2]. This arteriopathy can cause both ischemic strokes as a result of hypoperfusion as well as intracranial hemorrhage due to the vulnerability of collateral circulation and the coexistence of aneurysms[3,4].

There are two hypotheses about the pathogenesis of the pathology, with different ages of presentation depending on the development mechanism. According to the congenital hypothesis, twig-like MCA results from a failure in the fusion of the multiple plexiform vessel networks constituting the primitive MCA[5]. The second hypothesis proposes that twig-like MCA is the secondary consequence of chronic MCA occlusion, and the adult age of diagnosis and clinical manifestations support this proposal[6].

The differential diagnosis of this entity includes slowly developing occlusive vasculopathy, and, in this regard, two essential entities, such as moyamoya disease (MMD) and moyamoya-like syndrome (MMS), should be considered[7,8].

Ischemic and hemorrhagic stroke may occur in patients with twig-like MCA, but also incidental diagnosis is possible[9].

Digital subtraction angiography is the gold standard in diagnosis[10]. It shows features of a plexiform network of vessels replacing the proximal trunk of the MCA, with distal branches of the MCA beyond this network being of normal caliber with anterograde flow[11]. Our study aimed to clarify the imaging concepts used in the twig-like diagnostic criteria that allow them to be differentiated from other vascular entities[12].

In addition, we provide cases and images from our hospital that support the concepts described.

Congenital etiopathogenesis

In the embryonic stage, the primitive MCA consists of multiple networks of plexiform vessels that fuse to transform into a normal MCA during development. As a result of the absence of the fusion process, a twig-like MCA presents a plexiform arterial network (PAN) of the M1 segment. As part of an alteration in embryonic development, there is a high coexistence with other intracranial vascular anomalies such as fenestrations, arterial duplications, or aneurysms[13].

Acquired etiopathogenesis

There is a broad description of cases in which the clinical manifestations and diagnosis are made in late adulthood. These cases are unlikely due to a persistent alteration since embryonic development but rather to an acquired anomaly associated with hypertension and atherosclerosis that, as a secondary consequence, ends in a unilateral chronic occlusion of the proximal segment of the MCA, with adjacent development of a plexiform network with preservation of the normal caliber of the distal M1 segment[14].

Methodology

The present study, conducted with meticulous care, aimed to determine the prevalence of certain clinical characteristics from an anonymized database, using a retrospective and descriptive approach. A total of 1,428 diagnostic angiographies performed between January 2010 and December 2023 at our diagnostic center were included.

The data were processed and anonymized to ensure patient privacy.

The analysis was performed using specialized statistical software to identify the prevalence of significant findings, both descriptively and inferentially.

Epidemiology

The prevalence rate of rete MCA in Asian and European literature has been reported between 0.1 and 0.67%[11,12,15].

All diagnostic angiographies performed at our center between January 2010 and December 2023 were reviewed. Only those in which a complete anterior circulation study had been performed were included. Three cases met all clinical imaging criteria, resulting in a prevalence of 0.21%.

Clinical manifestations

Our literature review identified 82 cases of twig-like MCA in 15 previous studies. Among 56% of the patients were female, with a mean age of 48 years ± 21.2 years. Most published cases were symptomatic at diagnosis (72/82, 87%). Headache was the most common presenting symptom, reported in 47% of patients, followed by paresis contralateral to the steno-occlusive artery in 23 patients (28%). Intracranial hemorrhage was more frequent than ischemic stroke, which was seen in 38%

and 27%, respectively. The coexistence of an intracranial aneurysm was described in 38% of cases[1,11,14,15].

Diagnostic imaging

At present, the gold standard test for a twig-like MCA remains the DSA[10]. However, in a complementary way, the computed tomography (CT) perfusion study can be useful to identify areas of hypoperfusion and detect areas of the MCA territory where compensatory mechanisms maintain adequate cerebral flow, providing indirect information on vascular reserve[11]. In addition, including magnetic resonance imaging (MRI) of the intracranial vessel wall, combined with magnetic resonance angiography, may further aid in the differential diagnosis of other unilateral intracranial vasculopathy, such as those causing MMS[7,8].

Angiographic criteria in the diagnosis of twig-like MCA

Angiographically, an abnormal PAN with multiple channels and a steno-occlusive change is observed in the proximal M1 segment of the affected MCA. Adjacently, the lenticulostriate arteries (LSA) arise from the PAN, whereas the distal branches of the MCA beyond the network maintain a normal vessel caliber with anterograde blood flow[11]. About the differential diagnosis, it is essential to highlight that in twig-like MCA, there is unilateral involvement of the MCA without involvement or progression toward the contralateral side[12].

Case reports

Here, we report two cases whose age of clinical presentation differs widely, suggesting a different pathogenic mechanism.

Case 1

The patient was a 52-year-old female with hypertension. She referred three episodes of focal seizures with alteration to the state of consciousness in the last year, so brain MRI and MR angiography were performed, finding an absence of the M1 segment of the left MCA with the persistence of plexiform network from LSA (Figs. 1 and 2), for which requests DSA under suspicion of moyamoya syndrome. DSA showed the presence of twig-like left MCA involving the entire M1 tract with anterior and posterior M2 branches arising independently of the network (Fig. 3). No polymorphism associated with MMD was identified, particularly without ring finger protein 213 mutation. A test for antinuclear antibodies was positive at a titer of 1:160 with a homogeneous-speckled pattern, but the remainder of the antinuclear-antibody screening (anti-double-stranded DNA, anti-Ro/SSA, anti-La/SSB, and anti-ENA) was negative. An antineutrophil cytoplasmic antibody test, rheumatoid factor, anticardiolipin antibodies immunoglobulin G and immunoglobulin M, venereal disease research laboratory, and HIV were all negative. Cerebrospinal fluid analysis was within normal limits.

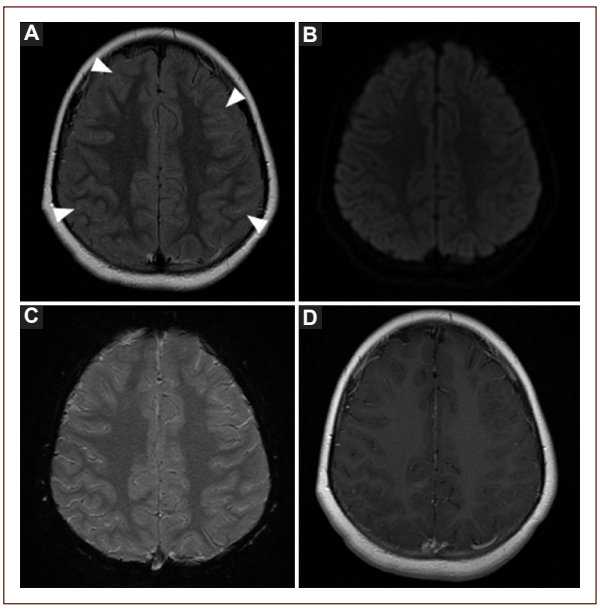

Figure 1. Brain magnetic resonance imaging. **A:** axial T2 fluid-attenuated inversion recovery shows subtle diffuse sulcal hyperintensity (white arrowheads), without parenchymal lesions. No abnormalities in **B:** diffusionweighted image; **C:** GRE T2-weighted image, and **D:** gadolinium-enhanced T1-weighted image.

Case 2

The patient was an 8-year-old male child. He presented a syncopal episode; upon regaining consciousness, weakness in the right lower extremity was evident for an hour and a half, with complete recovery. CT angiography showed an irregularity of the right proximal MCA, so he was referred for a complementary imaging study. DSA revealed a rete MCA anomaly at the right M1 (Fig. 4), and CTP showed hypoperfusion of the right hemisphere.

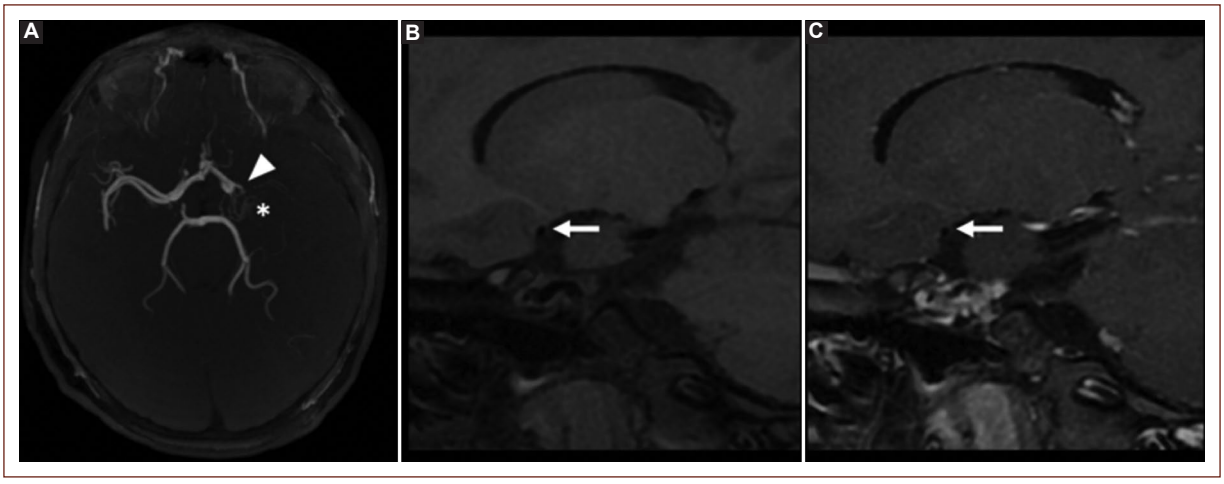

Figure 2. Magnetic resonance imaging. **A:** axial 3D time of flight maximum intensity projection image shows flow signal absence in the M1 segment of the left cerebral media artery (white arrowhead), associated with fine vessels forming a rete mirabilis (white asterisk). Three-dimensional (3D) variable-flip-angle turbo-spin-echo (CUBE) T1-weighted sequence with fat suppression, before **(B)** and after gadolinium administration **(C)**, shows no enhancement of the left cerebral media artery wall (white arrow).

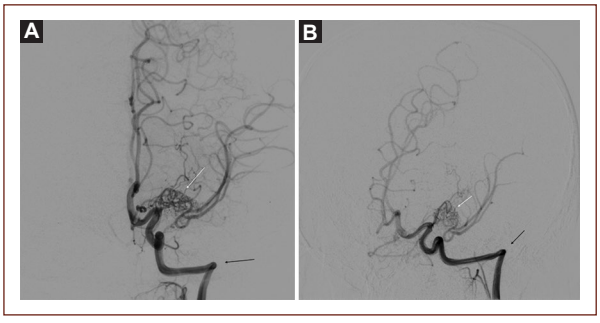

Figure 3. Digital subtraction angiography. **A:** antero-posterior proyection. **B:** oblique proyection, twig-like rete in M1 segment with normal Silvian distal (white arrow) and aberrant internal carotid artery (black arrows).

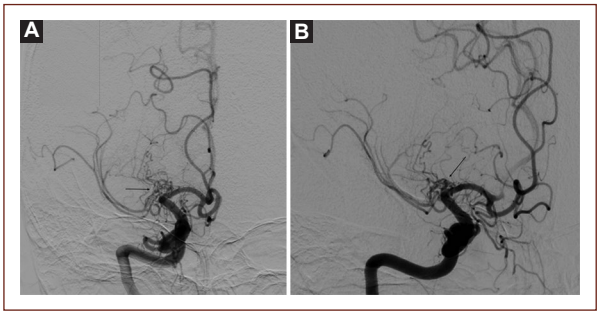

Figure 4. Digital subtraction angiography from a right internal carotid artery injection in anterior-posterior **(A)**, and oblique views **(B)**, showing right twig-like middle cerebral artery and the lateral lenticulostriate arteries arising from the network (black arrows).

Discussion

Knowledge of the variations of MCA, its incidence, and natural history is essential to make the appropriate diagnosis, in which DSA is clarifying, showing a more precise resolution of the anatomy, demonstrating an absence of internal carotid terminus and posterior cerebral artery involvement[1]. This will aid in distinguishing it from moyamoya angiopathy that may be present, thereby guiding the management of subsequent care and necessary treatment. Conversely, it helps in steering clear of ineffective and hazardous procedures[14].

The reason for requesting the angiographic procedure in 100% of the cases was moyamoya-like or moyamoya syndrome. This diagnosis was suspected by the referring doctor after a non-invasive imaging study, so it seems essential to disseminate the differentiating criteria within these pathological entities[15].

In our small case series, we present the broad age spectrum in which a twig-like MCA can be detected, highlighting one of the cases of younger age at the time of diagnosis, which increases the probability that it is associated with a congenital etiopathogenic mechanism. Diagnosis at an early age requires follow-up during the different stages of life since the compensatory mechanisms that develop during the embryonic stage and childhood could falter with the dynamic changes in circulation over time. Non-invasive monitoring makes it possible to predict claudication of the hypoperfused territory and to be able to perform a timely intervention[16]. It also seems essential to

identify concomitant vascular anomalies, especially aneurysms, since these have a higher prevalence in patients diagnosed at an early age, which correlates with a high cumulative incidence of hemorrhagic complications[17,18].

The prevalence calculated in our anonymized database was 0.21%, which is within the range described in the literature for Asian populations and noticeably different from other Latin–American studies. This variation may be attributed to the ethnic heterogeneity between the Argentinian and Chilean populations. Argentina experienced significant European migration between 1857 and 1960, primarily from Italy and Spain, which contributed to a genetic makeup comprising approximately 76% European, 17% Native American (NA), and 4% African ancestry in the Buenos Aires sample population[19]. In contrast, the Valparaiso, Chile sample population (our study site) consists of 57.11% European, 40.43% NA, and 1.97% African ancestry[20,21].

Interestingly, if we consider that NA populations originated primarily from Siberia and, as recent findings indicate, also from East China based on mitochondrial DNA lineage D4h studies, the higher NA component in our population could explain the observed prevalence being closer to that of Asian populations[22].

Conclusion

Twig-like MCA is a rare vascular anomaly whose prevalence in our series is similar to that reported in the literature. DSA is essential for diagnosing and approaching this pathology's etiopathogenesis.

Funding

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

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

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

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REVIEW ARTICLE

Comprehensive approaches in Alzheimer's disease: from general aspects to stem cell therapy and antidiabetic use

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid-ß and Tau protein in brain tissue. AD represents 80% of the cases of dementia worldwide, affecting more than 7.29 million people with an increase in incidence of 147.95% in the past 30 years. At present, conventional treatments for this condition remain limited, which has led to a significant increase in its incidence and prevalence. In this paper, we address general aspects regarding AD, from its pathophysiology, diagnostic methods, and its association with insulin resistance; as well as present treatments and new alternatives, specifically hypoglycemic agents, such as metformin, liraglutide and insulin; and neural stem cells. It is concluded that stem cell and antidiabetic treatments had positive results in preclinical studies, so more future studies are required to consider them safe in humans.

Keywords: *Alzheimer's disease. Stem cells therapy. Genetic factors and insulin resistance.*

Enfoques integrales en la enfermedad de Alzheimer: desde aspectos generales hasta la terapia con células madre y el uso de antidiabéticos

Resumen

La AD es una enfermedad neurodegenerativa progresiva caracterizada por la acumulación de placas de Aß y de proteína Tau en el tejido cerebral. La AD representa el 80% de las etiologías de demencia afectando a más de 7.29 millones de personas con un incremento del 147.95% en su incidencia. Actualmente los tratamientos convencionales para esta condición siguen siendo limitados, lo que ha conllevado al aumento en su incidencia y prevalencia. En este texto abordamos generalidades de AD, desde su fisiopatología, métodos diagnósticos y su relación con la resistencia a la insulina; así como tratamientos actuales y nuevas alternativas, específicamente hipoglucemiantes como la metformina, liraglutida y la insulina, y células madre neurales. Se concluye que los tratamientos con células madre y antidiabéticos tuvieron resultados positivos en estudios preclínicos, por lo que se requieren más estudios futuros para poder considerarlos seguros en humanos.

Palabras clave: *Enfermedad de Alzheimer. Terapia con células madre. Factores genéticos y resistencia a la insulina.*

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Introduction

Alzheimer's disease (AD) is defined as a type of dementia characterized by gradual and progressive neurodegeneration secondary to neuronal death[1]. Among the etiologies of dementia, approximately 80% are attributed to AD, making it the most prevalent type worldwide[2,3]. Trends in AD show a 147.95% increase in its incidence from 1990 to 2019, with 7.29 million cases worldwide in 2019[4]. This makes it one of the most significant chronic pathologies in terms of mortality, quality of life, and public health over the past century[5].

AD is a multifactorial condition, with age being the most significant risk factor for its development. The prevalence of AD tends to double every 5 years after the age of 65[6]. According to the Global Burden of Diseases, patients aged 70-74 show the highest incidence of AD. The aging population and increased life expectancy are the main contributors to the rise in the incidence of this pathology in recent years. It is estimated that by 2050, 152 million people will be living with AD worldwide[4]. The pathophysiology of AD involves environmental, genetic, and lifestyle factors[2]. While age is the most significant risk factor for AD, other identified risk factors include hypertension, obesity, diabetes mellitus (DM), physical inactivity, hearing loss, smoking, low educational attainment, social isolation, high alcohol consumption, traumatic brain injury, and environmental pollution[7].

Despite currently available treatments, AD remains a progressive condition for which there is no prevention or cure. So far, no treatment has advanced from being symptomatic to having an effect on the prognosis of the disease[3]. This work aims to provide a comprehensive review of the present knowledge on AD, diagnostic methods, treatments, and potential tools under study that show promising results for patients with this disease.

Generalities of AD

Pathophysiology

AD is a progressive neurodegenerative condition mainly affecting older adults, characterized by a decline in cognitive and functional abilities, along with behavioral changes. The disease progresses over 15-25 years, during which patients transition from normal cognitive function to dementia. During the early stages, patients may remain asymptomatic or experience mild to moderate neurocognitive impairment[5].

The pathophysiology of AD involves multiple biological processes, with the amyloid-ß (Aß) cascade hypothesis being widely accepted[8]. Abnormal processing of amyloid precursor protein (APP) leads to the formation of Aß plaques, which accumulate in the brain, causing synaptic dysfunction and neurodegeneration[9]. In addition, tau protein abnormalities and neurofibrillary tangles are also key pathological features that disrupt neuronal function and further exacerbate disease progression[2,8].

Genetic factors

Genetic factors significantly influence both early and late-onset AD[10]. Mutations in the APP, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes contribute to abnormal Aß plaque production, leading to inflammation, neuronal toxicity and death[3,5,9,10]. These mutations, following an autosomal dominant pattern, are responsible for familial AD, a rare form affecting 0.5% of cases, with symptoms typically appearing between ages 30 and 50. However, not all variants of these gene mutations result in familial AD, some may act as disease modifiers[5,9]. Among the genes associated with this disease, *PSEN1* mutations on chromosome 14 are the most prevalent (71.24%), followed by APP (46.97%), and *PSEN2* (20.63%)[11].

Another mutation associated with the development of AD is that of apolipoprotein E (ApoE), located on chromosome 19, with three isoforms identified: ε2, ε3, and ε4[12]. The mutation of the ε4 allele of the ApoE gene has been identified as the most significant genetic risk factor for both early and late-onset AD, occurring in approximately 65% of cases[1,12]. Carriers of one or two copies of the ε4 allele have a higher risk of developing the disease[1,10].

Inflammatory processes in AD

Inflammatory processes are key in AD development, involving astrocytes, microglial cells, cytokines, and chemokines that trigger neuroinflammation[13]. This inflammatory response damages the neuronal environment, contributing to oxidative stress and cellular apoptosis, leading to the onset of characteristic AD symptoms[14]. Neuroinflammation is a specific and enhanced immunological, biochemical, and hematological response that can be triggered locally or systemically. This process is a reaction to tissue or organ damage, designed to neutralize harmful factors and stimulate repair processes[15].

The most important substances exerting a pro-inflammatory effect in the brain and the body include cytokines (Interleukin-1 [IL-1ß], IL-6, IL-18, Tumor necrosis factor-α, Interferon-γ), chemokines (CCL2, CCL3, CXCL8), complement components (C1q, C5), transcription factors (NF-κB), peptides (bradykinin), enzymes (COX-2, iNOS, LOX), and coagulation factors platelet activating factor. Conversely, anti-inflammatory effects are exerted by lipoxins (LXA4, RvE1) and some cytokines (IL-10, IL-37, transforming growth factor-ß)[12]. In classical inflammation, the process is characterized by an increased secretion of pro-inflammatory mediators and a reduction of anti-inflammatory substances. To resolve the inflammatory response, the opposite occurs, pro-inflammatory substances decrease, and anti-inflammatory substances increase. Neuroinflammation in AD differs from peripheral inflammation. In the brain, neuroinflammatory factors, such as cytokines and chemokines can persist longer and display different dynamics compared to those in systemic inflammation[16].

Diagnostic methods

The diagnosis of AD is a complex process, requiring the evaluation of the patient's medical history, physical and neurological examinations, neuropsychological tests, and imaging studies. There is no single test that can definitively diagnose AD, therefore, the diagnosis is based on a combination of these different approaches[16]. Regarding medical history, the physician will review the patient's medical background, including any memory, behavior, or language problems, as well as family history. Neuropsychological tests are used to assess the patient's cognitive abilities, such as memory, attention, language, and problem-solving. These tests can help identify specific areas of cognitive impairment that may be associated with AD[17]. Imaging tests, such as positron emission tomography and magnetic resonance imaging, can help visualize the brain and detect changes that may be associated with the disease. These tests can help rule out other causes of dementia and determine the severity of the disease[18].

Conventional treatment

The treatment approach for AD is symptomatic, as there are currently no curative or prognosis modifier treatments[3]. Conventional pharmacological treatment focuses on cognitive improvement and the regulation of neuropsychiatric symptoms[5]. At present, there are two groups of drugs approved for use in AD: Acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists[9].

Relationship between insulin resistance and AD

The global increase in DM and AD has posed a major challenge for people, healthcare systems, and governments worldwide. Conventionally, studied separately due to the peripheral implications of DM and the central implications of AD, the growing prevalence of these conditions has led to a deeper exploration of their interconnected pathophysiology, particularly their shared pro-inflammatory underpinnings[19]. DM is a systemic, chronic-degenerative disease that is closely related to lifestyle and profoundly affects the quality of life of millions of people worldwide. Expected to reach a prevalence of 10.9% by 2045, DM manifests itself in three main types: Type 1, type 2, and type 3. Type 1 DM (DM1) results from the destruction of pancreatic β-cells, while type 2 DM (DM2) is due to impaired insulin resistance and secretion[20]. Type 3 DM (DM3) is a relatively new concept characterized by brain insulin resistance caused by the presence of metabolic syndrome and microglial inflammation induced by reactive oxygen species and neurotoxins, leading to neuronal stress and neurodegeneration[21].

There are two mechanisms by which DM2 increases the risk of damage to neurons, neuroglia, and the neurovascular unit of the brain: (1) neuronal senescence (complications in patients older than 65 years) and (2) metabolism (hyperglycemia and hyperinsulinemia, increased Aß toxicity, Tau hyperphosphorylation, oxidative stress, and neuroinflammation[19,21]. This metabolic state may lead to impaired neuronal function and cognitive impairment. This metabolic dysregulation further contributes to the formation of neuritic plaques, hippocampal atrophy, and lower cerebrocortical glucose metabolism, which is closely related to memory decline[20,19]. Kapogiannis et al. have demonstrated that at elevated levels of p-Ser312IRS1 (a kinase involved in autophagy) in patients with prodromal AD, suggesting that insulin resistance may develop years before clinical symptoms appear[22].

In addition, neuronal-derived exosomes have shown promise as potential biomarkers for early diagnosis of AD[23]. Defective insulin signaling in the brain in AD and DM2 may result from several factors, including insulin resistance, negative regulation of insulin receptors (IR), reduced binding affinity, or faulty activation of the

downstream signaling cascade[24]. Ultimately, this leads to a decrease in neuronal glucose uptake, manifesting as a decline in neuroplasticity, neurotransmitter deficiencies, bioenergetic collapse, and the onset of a detrimental inflammatory cascade. The disruption of insulin signaling alters brain metabolism, potentially paving the way for neurodegeneration and providing a compelling explanation for the link between DM, obesity, and AD[23,24].

Insulin and insulin-like growth factors (IGF-1) exert their effects by binding to specific tyrosine (Tyr) kinase receptors, such as the IR and the IGF-1 receptor. While the highest expression of IRs is observed in the olfactory bulb, cerebral cortex, and hippocampus, they are also present in the endothelial cells of the blood-brain barrier (BBB). This specific localization of IRs plays a crucial role in mediating the transport of insulin and IGF-1 across the BBB, thereby influencing the function of the central nervous system (CNS)[25].

Pancreatic β cells within the islets of Langerhans produce insulin, its effect by binding to transmembrane glycoprotein receptors composed of α and β subunits. These bindings are facilitated by disulfide bonds within the insulin molecule[26]. The initial step in insulin signaling involves the binding of the ligand and insulin to the extracellular α subunits of the IR, a transmembrane glycoprotein receptor complex composed of two α subunits and two β subunits. This binding event triggers conformational changes within the receptor, leading to the activation and autophosphorylation of specific Tyr residues located in the cytosolic region of the β subunit[27]. These phosphorylated residues then serve as binding sites for the substrates of the IR, particularly Insulin receptor substrate 1 (IRS-1) and IRS-2, which act as crucial intermediaries in the propagation of the insulin signal[28]. The assembly of these IRS-containing complexes orchestrates the initiation of multiple intracellular signaling cascades[25]. The hyperinsulinemia pathway (a state of excessive circulating insulin) is linked to AD due to the saturation of insulin-degrading enzymes, which hampers their ability to eliminate both insulin and Aß peptides, the latter being a hallmark of AD pathology. The higher incidence of AD in individuals with type DM2 and obesity further strengthens the notion of shared mechanisms[29]. Notably, although neuronal glucose uptake may not be entirely reliant on insulin, the notion of “brain insulin resistance” underscores the disruption of insulin signaling pathways. This disruption is increasingly recognized as a key factor in the pathogenic pathway between AD and DM2[23].

New treatments

Antidiabetic pharmacological agents for Alzheimer

Oral hypoglycemic agents that target insulin resistance in the brain by promoting proper incretin and insulin signaling are currently a promising option for the treatment of AD and other neurodegenerative diseases. Glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated neuroprotective and anti-inflammatory properties, with expression observed in neurons and glial cells[30]. GLP-1 receptors activate a series of anti-inflammatory pathways by stimulating adenylyl cyclase, which increases cAMP concentrations. This activates other cofactors that have an anti-apoptotic effect. In addition, various genes, such as Bcl-2, are activated, which are neuroprotective and inhibit the activation of pro-apoptotic proteins, such as caspases and p53[30,31].

Insulin, a hormone that regulates peripheral glucose homeostasis, also has significant implications for the nervous system. It swiftly crosses the BBB and can be synthesized by glial cells[32]. Although cerebral glucose metabolism is not dependent on insulin, this hormone can influence glucose concentrations through neuronal glucose transporter 4 in cognitive circuits and enhance glycogen absorption in astrocytes. In addition, insulin modulates neurotransmitter levels, such as dopamine, provides protection against the synaptotoxic effects of Aß, and plays a crucial role in vascular function due to its involvement in lipid metabolism and inflammation[32,33]. These attributes suggest that insulin may offer a therapeutic alternative for diabetic patients with cognitive impairment or AD.

Hypoglycemic agents in the treatment of AD

The research on specific drugs for AD treatment remains in its early stages, offering promising potential for reducing the degenerative damage caused by AD. Among the hypoglycemic agents studied are Metformin, the most commonly prescribed antidiabetic drug, and liraglutide[33]. Zheng et al. carried out a Mendelian randomization study on 527,139 Europeans from the general population, of whom 71,880 were either diagnosed with or at risk of developing AD. The study identified 22 metformin-related genes across 5 targets associated with the glycemic marker hemoglobin A1C, with brain connections confirmed through 6,601 brain donors, showing that 20 of the 22 genes were linked to the cerebral cortex and cognitive function. Results indicated that metformin use reduces the risk of AD by 15% in

Table 1. Mechanisms of action of antidiabetic agents with potential neuroprotective effects in Alzheimer's disease

Drug	Mechanism of action	References
Metformin	Reduces Aß levels and amyloid plaque formation, decreasing neuronal degeneration and cognitive decline	35
Liraglutide	Promotes the activity of the insulin signaling pathway Akt, preventing tau phosphorylation. GLP-1 receptors activate a series of anti-inflammatory pathways with anti-apoptotic effects. Various genes, such as Bcl-2, which are neuroprotective, are activated, and pro-apoptotic proteins are inhibited	30,31,37
Insulin	Modulates neurotransmitter levels such as dopamine, providing protection against the synaptotoxic effects of amyloid-beta protein	32,33

GLP-1: glucagon-like peptide-1; Aß: amyloid-ß.
Metformin, liraglutide, and insulin have demonstrated promising effects in preclinical models of Alzheimer's disease. These include reduction of amyloid-beta accumulation, anti-inflammatory activity, and modulation of neurotransmitter systems relevant to cognitive function.

diabetic individuals and by 4% in healthy individuals[34]. In a mouse model, metformin was found to promote chaperone-mediated autophagy, a process related to the pathophysiology of neurodegenerative diseases. AD is marked by progressive neuronal loss and Aß peptide oligomerization, resulting in amyloid plaque formation. Metformin has been shown to reduce Aß levels, leading to decreased cognitive impairment, delayed aging, and alleviation of age-related diseases[34,35]. Another antidiabetic drug that has shown evidence in reducing neurodegeneration is liraglutide, a GLP-1 inhibitor[34]. This medication may promote the development of stem cell stimulants, potentially leading to the proliferation of new neurons. In mouse models, it has been associated with calorie restriction, which decreases the amount of Aß plaques and neurofibrillary tangles. The use of GLP-1 reduces food intake and hunger. A mouse model study used liraglutide treatment for 2 months and found improvements in spatial memory and a 30%-50% reduction in inflammation[36]. Peripheral intravenous liraglutide demonstrated stimulation of the insulin Akt signaling pathway, preventing tau phosphorylation and reducing GSK3ß activity in mice[37] (Table 1).

Stem cell therapy in AD

The pharmacological treatments currently used for AD have certain limitations in managing the disease, as they show poor response in altering its progression. This has led to the ongoing search for new therapies to improve the quality of life for patients. Since there is currently no cure for AD, only disease-modifying treatments, the use of stem cells has recently been promoted as a therapeutic approach. Specifically, neural stem cells (NSCs), induced pluripotent stem cells (iPSC), and mesenchymal stromal cells (MSC) have shown promise in this area[38,39].

NSCs

NSCs are a type of multipotent stem cell, considered primitive cells with the ability to differentiate into various specialized cell types, give rise to other cells, and self-renew. These cells can generate different cell types in the CNS such as glia, neurons, and oligodendrocytes[38,40]. Due to these properties, NSCs have been investigated for their potential benefits in AD. NSCs are essential for CNS recovery in neurodegenerative diseases associated with oxidative damage, as seen in AD. The mechanism of action of these cells involves identifying the injury site and differentiating into astrocytes, neurons, and oligodendrocytes to adapt and promote cellular plasticity. In addition, they can reduce inflammation[41]. Endogenous activation or exogenous infusion of NSCs restores neural networks in the brains of AD patients, regenerates damaged areas, and plays a crucial role in cognition and memory. The transplantation of NSCs aims to enhance neural connections, improve the inflammatory environment of the brain secondary to AD, and regenerate the neural network that undergoes degeneration through the secretion of chemokines[41]. The use of NSCs *in vitro* has been shown to generate cholinergic neurons that improve memory performance, enhance cognitive function, reduce neuroinflammation, and increase neurogenesis in rodent models of AD[39]. In addition, the administration of these cells improves the migration, survival, and differentiation of neuronal cells, thereby enhancing memory[40]. Further clinical studies are needed to assess their efficacy in AD patients.

iPSC

iPSC have been significant since their first mention in 2007[42], particularly in the analysis of the pathogenesis of diseases influenced by genetic and environmental

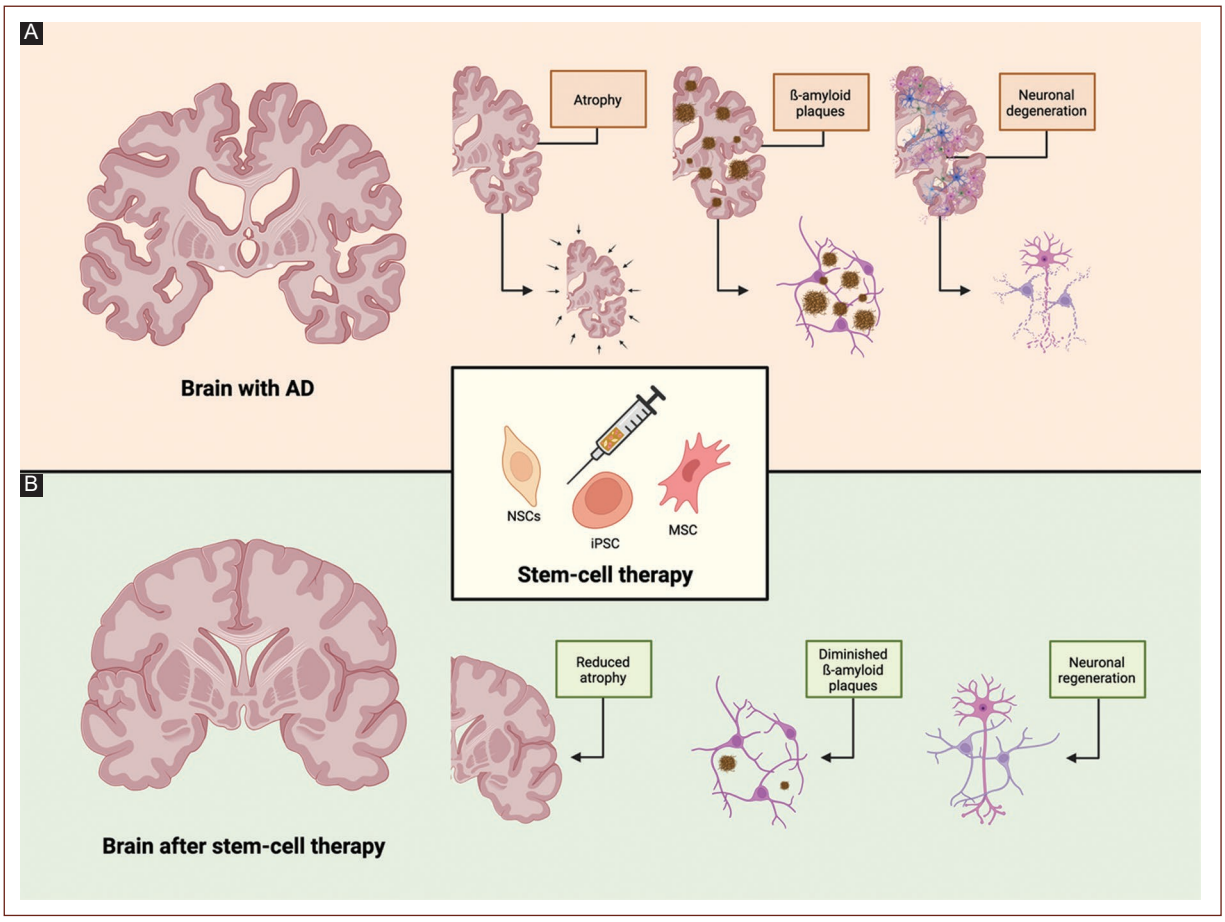

Figure 1. Pathological changes in the brain affected by Alzheimer's disease and the potential reparative effects of stem cell therapy. Panel A illustrates the hallmark neurodegenerative features of Alzheimer's disease, including progressive cerebral atrophy, the accumulation of ß-amyloid plaques, and widespread neuronal degeneration, all of which contribute to cognitive decline. These pathological changes are closely linked to elevated levels of neuroinflammatory cytokines and synaptic dysfunction. Panel B shows the potential therapeutic effects of stem cell-based interventions, including the administration of mesenchymal stromal cells (MSCs), induced pluripotent stem cells (iPSCs), and neural stem cells (NSCs). Following treatment, the AD brain demonstrates significant improvements: reduced cortical atrophy, decreased ß-amyloid plaque load, and signs of neuronal regeneration. The stem cell therapy may mediate their neuroprotective effects through several mechanisms: (i) differentiation into neural cell types, (ii) modulation of the neuroinflammatory environment, and (iii) enhancement of synaptic plasticity and tissue repair. Collectively, these actions support the structural and functional recovery of the AD-affected brain.

predispositions, such as age. Their application in neurodegenerative diseases is primarily focused on pathological research and the development of new drugs[43]. Their continuous differentiation potential into the three germ layers makes iPSCs a valuable source for managing various diseases[44]. Derived from the somatic cells of patients or healthy individuals, iPSCs have been demonstrated to be reprogrammed and differentiated into brain-specific cells, such as neurons, astrocytes, microglia, oligodendrocytes, pericytes, and vascular endothelial cells[45]. This capability facilitates the replacement of lost cells, the release of trophic factors and extracellular matrix, and the improvement of the aging environment through neuroprotection and inflammation suppression, ultimately leading to enhancements in neurodegenerative diseases[43]. This new technology continues to advance not only in the field of AD but also in Parkinson's disease, Amyotrophic Lateral Sclerosis, and Fibrodysplasia Ossificans Progressiva[43]. Although iPSC models have not yet reached the gold standard, they offer numerous advantages over other models in understanding the pathological mechanisms of AD[45]. In the case of these diseases, conducting precise analyses in animal models is challenging due to the

complexity of recreating pathological phenotypes that accurately mimic neurodegenerative diseases[43].

MSC

MSC exhibits typical stem cell characteristics, such as the ability to differentiate into various cell lineages[46]. They have played a significant role in correcting neurodegenerative disorders due to their active migration to damaged sites (homing), immunomodulatory and neuroprotective effects, as well as their roles in cellular repair and angiogenesis[46,47]. The ability of MSC to promote tissue repair through paracrine factors such as growth factors and cytokines allows modulation of the pro-inflammatory response, creating a conducive environment for neurogenesis and improving neurological deficits. Therefore, they are recognized as an innovative therapeutic option for inflammatory and chronic degenerative diseases[46]. MSC are attracted to sites of inflammation and can be obtained from various tissues such as bone marrow, adipose tissue, umbilical cord, amniotic fluid, placenta, and peripheral blood. When administered systemically, they cross the BBB, facilitating the elimination of Aß plaques, promoting neurogenesis, and reducing apoptosis. They also have the capacity to provide a healthy supply of mitochondria to the CNS, thereby mitigating the effects of aging and mitochondrial dysfunction related to AD. These actions can improve neuronal morphology and enhance spatial behavioral memory[48,49]. Studies in animal models of AD have confirmed the therapeutic potential of MSC. When administered to the brains of mice with AD, MSC secrete cytotropic factors–proteins capable of influencing cell growth and survival–rather than differentiating into neurons and glial cells, which can address multiple pathogenic mechanisms of AD[50]. In a study by Cone et al. MSC treatment significantly improved mouse memory and decreased the number of Aß plaques in the hippocampus[51]. In clinical studies, the primary focus is on evaluating the safety and toxicity of treatment doses. While some studies have observed elevated serum levels of biomarkers in control groups, such as vascular endothelial cells, IL-12, IL-10, IL-4, IL-6, and IL-2, which collectively promote an anti-inflammatory environment, transient fever has also been reported after each administration[52] (Fig. 1).

Conclusion

AD is a multifactorial disease with a complex pathophysiology. While there are many pharmacological treatments available, these drugs are limited to only improving symptoms and slowing disease progression and curative treatment for this disease is still lacking. Scientific information is constantly evolving, and in our article, we discuss the conventional treatment of AD and the present and future perspectives on the use of antidiabetics and stem cell therapy as promising therapeutic options in humans.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

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

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

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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