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Recommended care for IDH-mutant low-grade gliomas in Mexico

Recomendaciones de manejo de gliomas de bajo grado con mutación de IDH en México

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The publication of the first Mexican consensus guideline for the management of IDH-mutant low-grade gliomas represents a valuable initiative. It reflects a multidisciplinary effort to standardize care in a complex field where diagnostic and therapeutic resources remain heterogeneous across the country. This first step is particularly relevant in Mexico, where the absence of national registries and limited access to advanced molecular diagnostics hinder the uniform application of international standards. The initiative deserves recognition as it establishes a foundation upon which future versions can continue to build.

The consensus embodies the collaborative spirit that is essential in managing these complex tumors. The document highlights some of the challenges inherent to this process. The classification of gliomas has evolved substantially with the World Health Organization 2021 update, and precise terminology is increasingly important to avoid confusion in both clinical practice and research. Concepts, such as the restriction of “low-grade glioma” to grade 2 tumors, or the need to distinguish the assessment of extent of resection in non-contrast-enhancing gliomas using Fluid-Attenuated Inversion Recovery rather than T1-enhanced sequences, illustrate how subtle but critical details can shape treatment decisions. Including these

clarifications in future iterations will strengthen the guideline and ensure its alignment with international references, such as European Association of Neuro-Oncology, Spanish Society of Medical Oncology – Spanish Group of Investigation in Neuro-Oncology, or National Comprehensive Cancer Network¹⁻⁴.

The epidemiological data presented are of great value, especially given the paucity of national registries. Still, they remind us of the urgent need for prospective, multicenter data collection that would allow Mexican figures to be compared more directly with international reports. Similarly, the discussion of clinical presentation could be complemented in the future with emphasis on seizures as the hallmark symptom of IDH-mutant diffuse gliomas, an aspect consistently observed in global series.

The guideline also opens the door to further discussion on the integration of advanced molecular markers and neuroimaging techniques. Future iterations could benefit from incorporating the prognostic role of methylated DNA-protein cysteine methyltransferase promoter methylation and specifying recommended methodologies for markers, such as 1p/19q or BRAF. Equally, advanced imaging tools, particularly multi-modal magnetic resonance imaging sequences and amino acid PET, deserve greater emphasis in future

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guidelines, given their established value not only in diagnosis and surgical planning but also in the follow-up of non-contrast-enhancing gliomas⁵.

Therapeutic recommendations are another area where future versions of the guideline may continue to evolve. The role of temozolomide in low-grade gliomas, the exploration of alternative schedules, such as dose-dense regimens, and the optimal duration of maintenance therapy remain subjects of ongoing discussion in the literature and in daily practice. Addressing these questions explicitly would help clinicians navigate decisions that frequently arise in the Mexican context and would align the consensus more closely with international experience, including the Spanish Group for Neuro-Oncology Research guidelines. Equally, the criteria for monitoring response and progression are moving toward frameworks designed specifically for non-contrast-enhancing gliomas³. The adoption of Response Assessment in Neuro-Oncology (RANO)-low-grade gliomas and the updated RANO would harmonize Mexican practice with global standards, facilitating comparability with clinical trials and ensuring patients benefit from the latest advances in response assessment⁶.

In summary, this first Mexican consensus represents an important step toward more standardized care in the management of IDH-mutant gliomas. Beyond its immediate recommendations, it provides a framework on which future updates can build, incorporating advances in molecular diagnostics, imaging, and therapeutic strategies. The value of such efforts lies in their ability to evolve over time, progressively bringing national practice closer to international standards while addressing the specific challenges of the Mexican healthcare context.

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Early stage occlusion of non-ruptured intracranial aneurysms using flow diverter devices in Mexico

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Abstract

Objective: The objective of the study was to describe the rate of embolization success, the risk of complications, and the functional outcomes in the first 6 months post-treatment in patients with non-ruptured intracranial aneurysms (IAs) using flow-diverter (FD) devices in Mexico. **Methods:** Longitudinal, retrospective study of patients with non-ruptured IAs who were treated at the National Institute of Neurology and Neurosurgery between November 2020 and April 2022. After treatment with FD, post-procedure control angiograms were performed 6 months later. The occlusion rate was evaluated using the O'Kelly-Marotta scale. **Results:** There were 23 patients – 2 of whom had two IAs – 20 women, with an average age of 51.4 years (± 13.3). A total of 19 saccular, 4 fusiform, and 2 dissecting IAs were treated. Measurements of the neck ranged from 1.9 to 19 mm. Angioplasties were performed as part of the procedure on four patients, and successful liberation was achieved after 23 procedures. Total occlusion was achieved in 14 IAs, and 3 had < 5% residual filling in the follow-up. Only three late procedural-related complications were found. **Conclusions:** The use of the FD devices in our population appears to be safe and to have a high level of effectiveness in early post-procedural months, supporting its use.

Keywords: Intracranial aneurysms. Blood vessel prosthesis. Interventional radiology.

Oclusión temprana de aneurismas intracraneales no rotos mediante dispositivos desviadores de flujo en México

Resumen

Objetivo: El objetivo del estudio fue describir la tasa de éxito de la embolización, el riesgo de complicaciones y los resultados funcionales en los primeros 6 meses posteriores al tratamiento en pacientes con aneurismas intracraneales (AI) no rotos que utilizaron dispositivos desviadores de flujo (DF) en México. **Métodos:** Estudio longitudinal y retrospectivo de pacientes con AI no rotos tratados en el Instituto Nacional de Neurología y Neurocirugía entre noviembre de 2020 y abril de 2022. Tras el tratamiento con DF, se realizaron angiografías de control posprocedimiento a los 6 meses después. La tasa de oclusión se evaluó mediante la escala de O'Kelly-Marotta. **Resultados:** Se incluyeron 23 pacientes (2 de ellos con dos AI), 20 mujeres, con una edad promedio de 51.4 años (± 13.3). Se trataron 19 AI saculares, 4 fusiformes y 2 disecantes.

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Las medidas del cuello oscilaron entre 1.9 y 19 mm. Se realizaron angioplastias como parte del procedimiento en cuatro pacientes, lográndose una liberación exitosa después de 23 procedimientos. Se logró una oclusión total en 14 aneurismas intracraneales, y 3 presentaron un llenado residual < 5 % en el seguimiento. Solo se detectaron tres complicaciones tardías relacionadas con el procedimiento. **Conclusiones:** El uso de dispositivos DF en nuestra población parece ser seguro y presentar una alta efectividad en los primeros meses posteriores al procedimiento, lo que respalda su uso.

Palabras clave: Aneurismas intracraneales. Prótesis vasculares. Radiología intervencionista.

Introduction

Interventional neuroradiology has proven to be an effective technique for treating intracranial aneurysms (IAs) with a higher level of safety than periprocedural clipping¹⁻⁴. However, the effectiveness of this method's occlusion threshold depends heavily on the aneurysm's morphology and location: large, giant, deep, "blister," and fusiform IAs, and those associated with segmental artery stenosis, only exhibit rates of complete obliteration in up to 33% of patients, and recanalization in up to 20% of cases with coils and stent technique⁵. Due to this, therapeutic alternatives that included the use of endoluminal implants were developed, leading to the creation of a low-porosity stent-type device known as a "Flow Diverter" (FD)⁶.

FD diminishes hemodynamic circulation as well as the peak and average amount of kinetic energy that is transferred from the parental artery to the intrasaccular dilation (i.e., aneurysm) during each heartbeat. This is accomplished by creating obstruction to the flow by the low porosity stent. Reduced flow results in progressive intrasaccular thrombosis, the development of scar tissue, and ultimately endothelialization both of the FD and of the neck of the aneurysm⁷. Later, over the course of days or weeks, a complicated platelet activation pathway gradually forms a stable thrombus. The reduction of the aneurysm's final mass effect is made possible by the thrombus's intrasaccular conversion to collagen⁸.

Numerous publications from multiple institutions reported early positive results using FD^{9,10}. In addition, although they are uncommon, complications such as infarctions, hemorrhages, and late aneurysm rupture may occur¹¹. The publications that have been made, however, relate to social and health environments that are different from those in middle- and low-income countries, where different outcomes may be possible due to different confounding factors.

The cost of these devices is frequently a subject of debate in low- and middle-income countries, where limited resources impair treatments. Success and complication rates in the early months may support their treatment. Therefore, our goal was to determine the

percentage of IAs that are completely occluded in the first 6th months post-treatment in patients using FD devices in a tertiary center in Mexico, as well as the functional outcomes and complications risk.

Methods

Between November 2020 and April 2022, a descriptive, longitudinal, retrospective study that included all patients with non-ruptured IAs treated with FD devices at the National Institute of Neurology and Neurosurgery (INNN) was conducted.

The inclusion criteria were: Patients over the age of 18, who had the following aneurysm characteristics: Non-ruptured IAs of any type (saccular, fusiform, and dissecting aneurysm) in the anterior circulation from segment C4 to the union of the middle cerebral artery, as well as aneurysm(s) located in the posterior circulation from segment V4 of the vertebral artery to the posteroinferior cerebral artery. Bouthillier classification of the internal carotid artery was used¹². Exclusion criteria were patients with contraindications for endovascular procedures due to non-suitable anatomy or contraindication to antiplatelet therapy, as well as patient with poor medication compliance.

Following the procedure, digital angiograms were performed on these patients at 6 months. Demographic factors studied included age, gender, hypertension, smoking, dyslipidemia, diabetes mellitus, obesity, and alcohol use.

The PREMIER study's recommendations were the main factor in the decision to place the FD¹³, as determined by the interventional neuroradiologist. According to Zubillaga's proposed classification, it was determined to be a wide aneurysm¹⁴ those IAs with necks larger than 4 mm, or by Debrun's proposed classification¹⁵ if the dome/neck ratio is < 2.

All patients received dual antiplatelet therapy (DAPT) 7 days before the intervention. The procedures were carried out under general anesthesia. The location of arterial access (femoral or radial) and the catheters used were determined by the interventionist based on the patient's anatomical characteristics, degree of tortuosity, and location of the aneurysm. To evaluate the

aneurysm morphology, perform its measures, establish a working projection, and determine the dimensions of the devices to be used, orthogonal measurements and three-dimensional acquisition were attained. With direct fluoroscopy, the controlled release of the device was carried out while paying attention to the proper positioning of the device's entire body relative to the artery wall and the adequate coverage of the aneurysm neck. The FD effect and proper flow through the stent were demonstrated in all patients using angiographic controls in working positions and then orthogonal positions. Cone beam computed tomography (CT) was acquired as per protocol after the endovascular procedure to detect any lingering hemorrhagic complications. The DAPT was continued in all patients for 6 months, and thereafter single antiplatelet therapy was continued indefinitely.

Two researchers with expertise in interventional neuroradiology reviewed all of the studies of digital subtraction angiography in the Carestream Primary Agricultural Credit Society digital imaging system. Before the placement of the FD, the characteristics of the IAs were evaluated by identifying its type (saccular, fusiform, dissecting, or blister), its morphology (regular, complex), its location, its measures (neck length, dome-neck ratio), and the number of identified IAs. Successful liberation was assessed, as was the diverter's appropriate adhesion to the parental artery walls, full neck coverage, and documentation of any angioplasty using a balloon if needed.

The aneurysm-related occlusion was evaluated with subsequent angiograms, and it was classified using the O'Kelly-Marotta (OKM) scale¹⁶. Its classifications are A: entire filling, B: partial filling (5-95%), C: entry remanent (< 5%), and D: no filling (0%). At the same time, this scale includes the degree of stasis found in the arterial (1), capillary (2), and venous phases (3). In addition, studies using cone beam CT (DYNA CT) were conducted to evaluate the presence of intimal hyperplasia.

The complications identified during clinical follow-up and imaging studies were classified as acute trans procedural or delayed complications (up to 6 months).

Outcomes were evaluated at 6 months. Efficacy outcomes were the degree of disability using the Modified Rankin Scale (considering a favorable outcome between 0 and 2); and the occlusion ratio assessed in angiograms using the OKM scale. Safety outcomes were mortality and complications related to the procedure (such as ischemic vascular events, bleeding from aneurysm rupture, and complications up to 1 month after the procedure).

The analysis included a description of the variables using frequencies and percentages (n, %) and medians

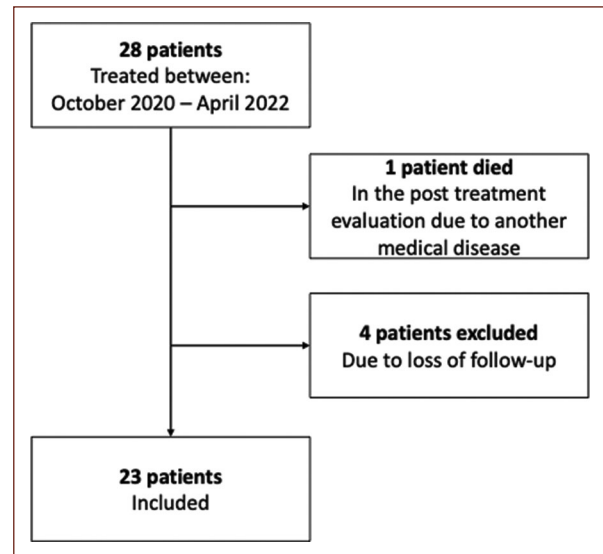


Figure 1. Study participant eligibility.

with interquartile ranges (IQR). Using Fisher's exact test and the statistical analysis application STATA 16.1, the comparison of the outcome of interest (complete occlusion to the 180 days) was carried out. The study has received approval from the INNN's Ethics and Research Committees for its execution, CEI/101/2022.

Results

Population studied

We identified 28 patients treated with FD, 26 of whom had unique IAs. One patient passed away from an undiagnosed metastatic prostate cancer, and four patients lacked follow-up angiograms for 6 months due to a variety of reasons (Fig. 1).

Risk factors studied

We found a gender and age trend, since 20 (87%) of the 23 patients who were included in the analysis were female, and the average age was 51.4 ($\pm$ 13.3 years). In this patient population, the most prevalent related disorders were obesity, dyslipidemia, and hypertension (Table 1).

Aneurysm characteristics

Two of the patients had two IAs each, making the total number of IAs treated 25: 19 (76%) saccular, 4 (16%) fusiform, and 2 (8%) dissecting IAs. These

Table 1. Demographics of the study population

Age (mean $\pm$ SD)	51.4 $\pm$ 13.3 years (%)
Female sex, n (%)	20 (87)
Clinical data, n (%)	
Hypertension	12 (52.2)
Diabetes mellitus	5 (21.7)
Dyslipidemia	9 (39.1)
Obesity	9 (39.1)
Smoking	4 (17.4)
Alcohol consumption	3 (13)
Modified Rankin scale, median (IQR)	0 (0-3)

SD: standard deviation; IQR: interquartile range.

latter two were located in the area of the vertebral artery. No “blister” type IAs were treated. In contrast to those typical aspect IAs without multiple lobes or “blebs,” whose morphology tended to be simple, 15 of our series’ IAs (or 60%) had complex morphology.

The measurements of the IAs’ neck sizes ranged from 1.9 mm to 19 mm. We identified 14 (73.7%) IAs with wide neck, of which 5 (20%) met the Zubillaga and Debrun criteria and 7 (28%) the Zubillaga definition. The overall number of saccular wide neck IAs throughout the series was 16/19 (84.2%). According to width length, the smallest aneurysm measured 1.5 mm and the largest was 29 mm. The overall number of saccular wide neck IAs throughout the series was 16/19. (84.2%). In the width measurements, the smallest aneurysm measured 1.5 mm and the largest was 29 mm. (IQR 5.3 mm) (Table 2).

The PREMIER study classified the cerebral aneurysm as being in the anterior or posterior circulation. In our study, the section most frequently affected in the anterior circulation contained 12 IAs in the paraclinoid segment (48%) of which 10 (40%) occurred in the ophthalmic segment (C6) and 2 (8%) in the clinoid segment (C5); in second place were 5 (20 %) IAs located in the communicating segment (C7). There were only 2 (8%) posterior circulation IAs, both in the intradural segment of the vertebral artery (V4). Other locations of the IAs are shown in table 2.

Aneurysm’s treatment

Fourteen (60.9%) IAs were treated with cobalt-chrome FD, of which 12 (52.2%) were Pipeline Shield® (Medtronic), and two (8.7%) were Surpass Evolve® (Stryker). Ten (43.5%) of the patients were treated with nitinol FD: 8 (34.8%) with Silk+® (Balt Extrusion) and

Table 2. Aneurysmal structural features and localization

Aneurysm morphology (n = 25)	
Saccular, n (%)	19 (76)
Fusiform, n (%)	4 (16)
Dissecting, n (%)	2 (8)
“Blister”, n (%)	0
Complex morphology, n (%)	15 (60)
Aneurysm measurements (n = 19) (mm)	
Neck width median (IQR) (min-max)	3.3 (2.0) (1.9-19.0)
Dome median (IQR) (min-max)	5.5 (5.3) (1.5-29.0)
Dome-neck ratio median (IQR) (min-max)	1.4 (1.2) (0.6-4.6)
Wide neck aneurysm, n (%)	16 (84.2)
Characteristics of fusiform and dissecting aneurysms (n = 6) (mm)	
Length median (IQR)	15.5 (13.8) (7.6-27.8)
Maximum diameter median (IQR) (min-max)	6.0 (5.8) (4.4-10.7)
Localization (n = 25)	n, (%)
Anterior circulation (n = 23) (%)	
ICA C4	1 (4)
ICA C5	2 (8)
ICA C6	10 (40)
ICA C7	5 (20)
MCA M1	4 (16)
MCA M2	1 (4)
MCA Bifurcation	0
ACoA	0
DACA	0
Posterior circulation (n = 2)	
Basilar	0
Vertebrobasilar union	0
Vertebral	2 (8)
PICA-Vertebral artery union	0

ACoA: anterior communicating artery; DACA: distal anterior cerebral artery; ICA: internal carotid artery; IQR: interquartile range; MCA: middle cerebral artery; PICA: posterior inferior cerebral artery.

two (8.7%) with FRED® (Microvention). FD diameters ranged from 2.5 to 5 mm (IQR: 1.25), and between 15 and 30 mm for their length (IQR: 2.0).

In two IAs (8.7%) it was necessary to telescoping two FD, both cases were fusiform aneurysm of the middle cerebral artery, both treated with nitinol FD Silk+® (Balt Extrusion). In 1 (4.3%) there were three telescoped FD to treat a fusiform aneurysm of the middle cerebral artery, all of them made of nitinol: 2 Silk+® (Balt Extrusion) and 1 FRED® (Microvention).

Outcomes

A successful liberation without stroke or hemorrhagic complications was achieved in 23 (100%) of the patients, with correct adhesion to the vessel wall in all of them. Incomplete neck occlusion, defined as the lack of the

attachment of the proximal third segment of the FD to the parental artery proximal to the aneurysm neck, was seen in 3 (13%) patients: One patient with a giant cavernous segment aneurysm which was also treated with coiling, another patient with a fusiform aneurysm of the middle cerebral artery, and one patient with a paraclinoid aneurysm in the C6 segment with a posterior circulation fetal pattern.

Four (17.4%) of the patients were treated with balloon angioplasty to assure adequate adhesion the arterial wall and to reduce the risk of stenosis: one patient with a fusiform aneurysm in the M1 segment of the middle cerebral artery treated with two telescoped FD, other patient with M1 segment aneurysm with a stenotic segment in the distal M1 segment, and in two patients with paraclinoid IAs (C6).

Follow-up

According to the OKM grading scale, 14 (56%) of the patients achieved D grade; 3 (12%) C grade. Occlusion results are shown in [table 3](#).

Thirteen (56%) patients were classified with a baseline mRs of 0, 5 (22%) with 1, and 5 (22%) with 2-3. At the 6 months follow-up, 16 (70%) were classified with 0, 4 (17%) with 1, and 3 (13%) with 3. In five cases (22%), the mRs at 3 months had improved by one point. There was no mortality associated with procedural complications.

There were not acute stroke or hemorrhagic complications during any of the procedures. Three (13%) patients developed late procedural complications: 2 (8.7%) with > 50% stenosis of the endoluminal area, both of which in the fusiform treated IAs of the middle cerebral artery; other patient with C7 segment of the left internal carotid artery with wide neck aneurysm presented FD migration toward the terminal portion of the internal carotid artery, who was scheduled for later retreating.

Discussion

This study comprises both anterior and posterior circulation IAs, with diverse morphology and defiant characteristics to the physician attempting coiling or clipping treatment, including dissecting, saccular, wide neck, and fusiform IAs. Our study is one of the earliest reports to come out of Mexico on the use of FD for treating intracranial non-ruptured aneurysm currently available.

The majority of IAs treated were saccular (76%) of which more than half (60%) had complex morphology

Table 3. Percentage of aneurysm-related occlusion according to the O'Kelly Marotta scale

Classification	n (%)
A1	0
A2	0
A3	2 (8)
B1	0
B2	1 (4)
B3	5 (20)
C1	1 (4)
C2	1 (4)
C3	1 (4)
D	14 (56)
Total	25 (100)

by displaying multilobular structures or blebs appearance; of these, we found wide neck aneurysm in 82.4% of the cases. According to the definitions of the Unruptured Intracranial Aneurysms study², 16 (64%) of the total of the aneurysmatic lesions were small saccular with a width ≤ 10 mm, of which 10 (62.5%) achieved OKM D grade. This is inconsistent with what was reported in the metanalysis of Yao et al.¹⁷, where the percentage of occlusion for cases of IAs with identical characteristics was 84.2%; although not far off from what was reported in 2020 by Fiorella et al. meta-analysis¹⁸, whom reported 75% occlusion rate in the 1-year follow-up for the small and middle non-ruptured IAs, with an 8% complication rate. In our study, seven IAs in this group had control angiography after 3 months, demonstrating a complete exclusion in three of them (42.9%).

Regarding saccular IAs, 2 were large (10-25 mm) and 1 was giant (> 25 mm) achieving complete occlusion in one case. One patient in this group displayed a FD migration complication. The total percentage of saccular IAs that were completely excluded was 57.9%, which suggests that our results are still below the average percentage. According to Cagnazzo review of the use of FD in ruptured IAs, immediate occlusion is achieved in 32% of the cases, and long-term occlusion was 89%, with a complication rate of 18%¹⁰, in contrast to Brinjikji⁹, which included ruptured and non-ruptured IAs, and evaluated a total of 1654 treated with FD, where occlusion rate was 76% and complication rate was 5%. These

differences may be due to the length of the study period given that we report occlusions after 6 months, when studies typically value this information annually, in addition to the center's characteristics, such as the number of patients treated, as well as the unique characteristics of the IAs, since these expensive and infrequent procedures are reserved for patients with more complex IAs and, thus, lower chances of complete occlusion.

These occlusion rates were obtained at 6-month follow-up and in patients with successful FD placement, similarly to what was reported by Lylyk et al.¹⁹, whom described 97% occlusion rate in the first series of IAs treated with the first-generation FD Pipeline®. Nevertheless, although high levels of occlusion were not achieved, our complications percentages were substantially lower, and our patient's late functional disability was low and dependent on their pre-existing conditions. These results are comparable to or less severe than those of larger retrospective studies²⁰.

In our geographical and socioeconomic environment, there are few studies that have assessed the outcomes of FD. A review from 2003 to 2023 found that in South America most of the reports of IA treatment that have been published correspond to the countries of Brazil, Argentina, Chile, and Colombia; however, not all of them used FD²¹.

In Peru, a study was published in 2023 with results of the use of FD in IAs in four tertiary care centers. A complete occlusion rate of 76% at 12 months was found. This study only included one type of FD²². One of the studies with larger samples was reported by Lylyk et al. (2021) in Argentina, which reported a complete occlusion rate of 75.6% in a population of 1000 IAs²³. In comparison to these reports, our study compared different types of flow diversifiers and their outcomes.

Studies have also been carried out in countries with limited resources but not geographically related populations, such as the African continent. Factors such as lack of access to specialized treatment clinics, post-operative mortality, and financial capabilities exert a burden on their patients²⁴.

A 2021 meta-analysis found an 85.6% occlusion rate in 1060 IAs treated using flow diversifiers with surface modifications²⁵. A 2023 meta-analysis found that occlusion rates at 1 year were 77%²⁶. Our study showed a lower percentage; however, it should also be considered that the response time evaluated was also earlier. This could guide subsequent reports with extended follow-ups.

Our study has some limitations, the first of which is that it only represents the local experience of one

single national center of reference in Mexico and cannot be generalized to other Latin American settings; however, our center is reference for several hispanic-speaking countries and has the highest case study rate in our region. Second, the sample size is small compared to other reported studies. In addition, due to the complexity of the cases received and the limited resources available, we choose to be as selective as possible and only include the most complex cases, which may imply selection bias. As a result, our results may not be equivalent to other studies with larger populations.

Conclusion

This study demonstrates that the embolization of intracranial non-ruptured IAs with FD stents is a safe and reproducible alternative with low associated morbidity rates and favorable success rates in the early post-treatment stage in a tertiary care center in Mexico, particularly in small-sized aneurysms with sacular morphology.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

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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Predictive model of mild neurocognitive disorder due to Alzheimer's disease in Cuban adults

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Abstract

Objective: Develop a predictive model for mild neurocognitive disorder (NCD) based on the risk factors for Alzheimer's disease (AD). The diagnosis of NCD associated with the presence of risk factors for AD is still incipient and requires greater diagnostic precision. **Methods:** A cross-sectional, analytical, observational case-control study was carried out in 100 subjects classified as mild NCD due to possible AD according to Diagnostic and Statistical Manual of Mental Disorders-5 criteria and twice controls with normal cognitive functions, aged 50-64 years and both sexes, selected by simple random sampling, during the period from January 1 to December 31, 2024. The variables that constituted prognostic factors were determined by multivariate binary logistic regression. **Results:** Low educational attainment, low skill level, physical inactivity, smoking, diabetes mellitus, hypertension, obesity, weight loss and COVID-19 were included in a model that explained 82.5% of the dependent variable (Nagelkerke's R^2); with 83% sensitivity and 95% specificity; calibration was good (Hosmer-Le-meshow test = 0.940) with an area under the receiver operating curve (AUROC) of 0.976 (95% confidence interval [CI]: 0.961-0.990). A risk score was calculated from the model, defining two categories: low risk (< 33) and high risk ($\geq$ 33), with an AUROC of 0.918 (95% CI: 0.877-0.958). **Conclusions:** The predictive model included nine variables that were easy to determine and interpret; therefore, it can constitute a useful tool in decision-making aimed at early and probably more effective interventions.

Keywords: Alzheimer's disease. Cognitive dysfunction. Risk factors.

Modelo predictivo de trastorno neurocognitivo leve debido a la enfermedad de Alzheimer en adultos cubanos

Resumen

Objetivo: Desarrollar un modelo predictivo de trastorno neurocognitivo leve basado en los factores de riesgo de la enfermedad de Alzheimer (EA). El diagnóstico de trastorno neurocognitivo asociado a factores de riesgo de la EA es incipiente y requiere gran precisión. **Métodos:** Se realizó un estudio observacional, analítico, transversal de casos y controles en 100 sujetos clasificados de deterioro neurocognitivo leve debido a la EA posible de acuerdo con criterios del Manual Diagnóstico y Estadístico de Trastornos Mentales (DSM-5) y 200 controles con funciones cognitivas normales, de 50 a 64 años y ambos sexos, seleccionados por muestreo aleatorio simple, durante el período del 1 de enero al 31 de diciembre de 2024. Las variables pronósticas se determinaron por regresión logística binaria. **Resultados:** Bajo nivel escolar, bajo nivel de

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competencias, inactividad física, tabaquismo, diabetes mellitus, hipertensión arterial, obesidad, pérdida de peso y COVID-19 fueron incluidos en un modelo que explicó el 82.5% de la variable dependiente (R^2 de Nagelkerke), con 83% de sensibilidad y 95% de especificidad, buena calibración (prueba de Hosmer-Lemeshow = 0.940) y área bajo la curva operativa del receptor (ABCOR) de 0.976 (95% CI: 0.961-0.990). Se calculó un puntaje de riesgo a partir del modelo, definiendo dos categorías: bajo (< 33) y alto ($\geq$ 33), con ABCOR de 0.918 (95% IC: 0.877-0.958). **Conclusiones:** El modelo predictivo incluyó 9 variables de fácil determinación e interpretación; por eso, puede constituir una herramienta útil en la toma de decisiones orientadas a intervenciones tempranas y probablemente más efectivas.

Palabras clave: Disfunción cognitiva. Enfermedad de Alzheimer. Factores de riesgo.

Introduction

Alzheimer's disease (AD) is the most common form of dementia and represents 60-70% of all cases, characterized by cognitive impairment of degenerative nature and progressive evolution¹. Although the prevalence of AD and other causes of dementia has increased in recent years², it presents a global underdiagnosis³. Cuban researchers locate the genesis of underdiagnosis in primary health care (PHC) to low prevalence of dementia (10.2% in people aged 65 years or older) and low incidence rate (21.7/1000)⁴. Diagnosis in the PHC is usually late (on average, 2 years before death), compared to hospital records⁵.

The late diagnosis of cognitive impairment is related to a low diagnostic capacity in adulthood⁶. It is favorable to diagnose AD in subclinical stages, even before mild cognitive impairment (MCI)^{7,8}. Early diagnosis allows the evaluation of reversible causes, improves the care of comorbidities, guides the selection of appropriate treatments, and identifies the need for social support, planning for the family, and the person themselves⁵.

Predictive models of the progression of MCI to AD^{9,10}, in patients with some degree of cognitive impairment aged over 65 years, could be too late for effective interventions due to the long subclinical progression of the disease. Other models describe MCI's prediction, which, despite their great sensitivity and specificity, present real limitations in low-income countries because some of their variables cannot be easily measured, such as eye tracking technology, concentration of amyloid protein in magnetic resonance scans, and $\epsilon 4$ allele of apolipoprotein E¹¹⁻¹³. Therefore, the development of new predictive tools with easy variables to determine and interpret is necessary, even in adults with normal cognitive functioning. The present investigation was carried out with the objective of developing a predictive model for mild neurocognitive disorder (NCD) based on the risk factors for AD.

Methods

Type of study

A cross-sectional, analytical, observational case-control study was carried out in patients of Manuel Fajardo Rivero Polyclinic, in the Cuban municipality of Las Tunas and province of the same name, during the period from January 1 to December 31, 2024.

Population

The population included 11,037 patients aged between 50 and 64 years old of the PHC Area, determined by dispensarization in 2023. The age range is under 65 years according to the average age of onset of AD suggested in the literature^{1,2,4-8}, to provide early diagnosis of the tool.

A random population sample of 97 subjects was estimated, using the GRANMO sample size calculator version 7.12¹⁴, from a population of 11,037 subjects, with an alpha risk of 0.05, precision of ± 0.1 in two-sided contrast for an estimated proportion of 0.5 and a replacement rate of 0%.

Those subjects who expressed their willingness to participate, with one or more AD's risk factors^{1,2,4-13} and other factors at the criteria of the authors according to their own systematic review, were included¹⁵. Included cases presented evidence of modest cognitive decline from a previous level based on: concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and a modest impairment in cognitive performance, documented by standardized neuropsychological testing. The cognitive deficits do not interfere with the capacity for independence in everyday activities¹⁶.

Subjects who did not cooperate with the neurological/neuropsychological examination and with evidence of mixed etiology (neurodegenerative or cerebrovascular disease, other neurological, mental or systemic disease,

or any other condition with a high probability of contributing to cognitive decline) were excluded¹⁶.

These inclusion and exclusion criteria were based on the diagnostic criteria for mild NCD due to possible AD, as described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders¹⁶.

Finally, from a group of subjects of the population with one or more AD's risk factors, 100 subjects with MCI were detected and twice as many normal cognitive functions controls were included from the rest, through simple random sampling (Fig. 1), with a median age of 58 years and male predominance (172/57.3%).

Variables

To describe the sample, 16 variables were studied.

Dependent variable: cognitive impairment. MCI was defined by a score of 70 and under in the neurocognitive evaluation, using the Cuban Addenbrooke's Cognitive Examination Revised (CACE-R), with reliable internal consistency (Cronbach's coefficient $\alpha = 0.879$) and optimal cutoff score of 84/85¹⁷. For the regression analysis, two categories were considered: (0) no and (1) yes.

Independent variables:

- Sex^{8,15}: (0) male, (1) female.
- Educational attainment^{8,15}: is the highest level of education that the person has completed, according to the levels of education in Cuba. For the regression analysis, two categories were considered: (0) for high educational attainment in the case of high school and university, and (1) for low educational attainment in the case of primary and middle levels.
- Family history of dementia^{8,15}: (0) no, (1) yes.
- Smoking^{8,15}: (0) no, (1) yes.
- Physical activity^{8,15}: (0) sufficiently active: 4 points and over, (1) insufficiently active: under 4 points, according to the Abbreviated Physical Activity Assessment Questionnaire for Primary Care (BPAAT) with a concordance coefficient k of 0.774 and high statistical significance and power ($p < 0.000$; 95% confidence interval [CI]: 0.69–0.85) with the International Physical Activity Questionnaire¹⁸.
- Social isolation^{8,15}: (0) not isolated: over 12 points, (1) isolated: 12 points and under, according to the criteria of the validated Spanish version of the six-item Lubben Social Network Scale¹⁹.
- Diabetes mellitus^{8,15}: (0) no, (1) yes.
- Hypertension^{8,15}: (0) no, (1) yes.
- Chronic kidney disease²⁰: (0) no, (1) yes.
- Obesity^{8,15}: BMI $> 30 \text{ kg/m}^2$: (0) no, (1) yes.

- Hypercholesterolemia²¹: (0) no, (1) yes.
- Weight loss²²: decrease in body weight of 2 kg and over or 5% and over in the previous 12-month period, not due to change in diet, physical exercise, bariatric surgery, or proven disease or cause: (0) no, (1) yes.
- Ischemic heart disease²³: (0) no, (1) yes.
- Skill level: it was defined as a function of the complexity and range of tasks and duties to be performed in an occupation according to criteria of the International Standard Classification of Occupations (ISCO-08)^{24,25}. Two categories were considered: (0) for high skill level in the case of 3 and 4 levels of the ISCO-08, with greater intellectual requirements, and (1) for low skill level: in the case of 1 and 2 levels of the ISCO-08, with a predominantly manual work activity.
- COVID-19^{26,27}: history of biomolecular diagnosis by polymerase chain reaction: (0) no, (1) yes.

Data processing and analysis

The data were obtained from the interrogation, physical examination, and clinical history. It was processed in Statistical Package for the Social Sciences, version 25 for Windows. The Chi-square statistical test was used based on its homogeneity hypothesis to determine the differences between the groups established according to qualitative variables.

A multivariate binary logistic regression analysis was implemented to determine the variables that constituted prognostic factors, which included those that had statistical significance in the univariate analysis. Variables with collinearity problems were not included in the model. For each independent variable in the model, more than 10 frequencies of the dependent variable were taken into account. Analysis was done with a reliability of 95%.

The omnibus test of the model was evaluated, and Nagelkerke's R^2 was analyzed for explaining the variance. The goodness of fit of the model was determined through the Hosmer-Lemeshow test. The variables whose coefficients were significantly different from 0 ($p < 0.05$) were identified using the Wald test. The discriminatory capacity was evaluated using the sensitivity and specificity values, positive predictive value (PPV), negative predictive value (NPV), receiver operating curve, and area under the curve (AUC).

From the results of the logistic regression, the odds ratios (OR) rounded to a whole number were taken as weights for each variable, $OR = \text{Exp}(B)$; in this way, the resulting predictive model was composed of a

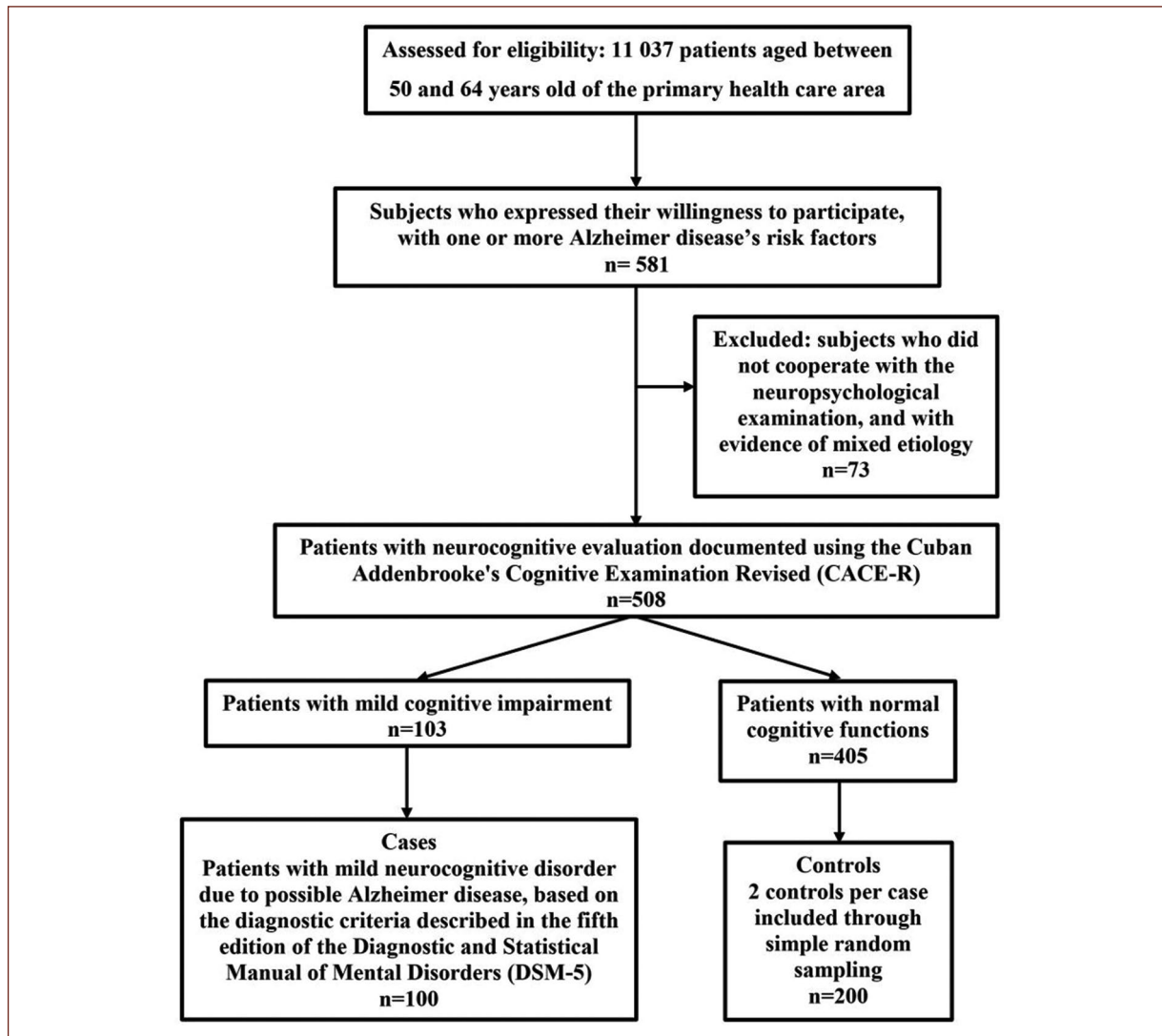


Figure 1. Flow diagram of participant selection.

global index in form of a linear combination: $I = x_1w_1 + x_2w_2 + \dots + x_kw_k$, where I constitutes the proposed model; k , the number of variables, x_k is the predictive variable; and w_k , the weight chosen for said variable in the model.

A risk score was calculated for each subject, with the 70th percentile of empirical values defining two categories: low risk and high risk, and its discriminatory capacity was evaluated similarly to the model.

Bioethical considerations

The investigation was carried out under the approval of the scientific council and the ethics committee of Manuel Fajardo Rivero Polyclinic. Participation in the

study was carried out under the principle of voluntariness, obtained through informed consent. It was accepted that the ethical principles for research in human beings, under the Declaration of Helsinki²⁸.

Results

Table 1 shows the distribution of clinical epidemiological variables in the two study groups. The group classified with MCI showed a significant predominance of low educational attainment, low skill level, physical inactivity, non-communicable chronic diseases (diabetes mellitus, hypertension, obesity), smoking, weight loss, and history of COVID-19 infection. Factors such as female sex, family history of dementia,

Table 1. Distribution of subjects according to clinical and epidemiological variables versus neurocognitive evaluation in univariate analysis

Variables	No cognitive impairment, n (%)	Mild cognitive impairment, n (%)	Total, n (%)	Sig.
Female sex	86 (43)	42 (42)	128 (42.7%)	0.869
Low educational attainment	50 (25)	75 (75)	125 (41.7)	0.000
Low skill level	54 (27)	91 (91)	145 (48.3)	0.000
Family history of dementia	11 (5.5)	6 (6)	17 (5.7)	0.860
Hypercholesterolemia	100 (50)	60 (60)	160 (53.3)	0.102
Physical inactivity	49 (24.5)	80 (80)	129 (43)	0.000
Social isolation	32 (16)	18 (18)	50 (16.7)	0.661
Diabetes mellitus	56 (28)	82 (82)	138 (46)	0.000
Hypertension	54 (27)	79 (79)	136 (44.3)	0.000
Chronic kidney disease	25 (12.5)	14 (14)	39 (13)	0.716
Obesity	25 (12.5)	52 (52)	77 (25.7)	0.000
Smoking	33 (16.5)	63 (63)	96 (32)	0.000
Weight loss	44 (22)	65 (65)	109 (36.3)	0.000
Ischemic heart disease	19 (9.5)	11 (11)	30 (10)	0.683
COVID-19	58 (29)	88 (88)	146 (48.7)	0.000

Sig: significance level from Chi-square statistical test.

hypercholesterolemia, social isolation, chronic kidney disease, and ischemic heart disease did not show significantly different frequencies between the control group and MCI patients.

Table 2 lists variables included in the binary logistic regression with $OR > 1$ ($p < 0.05$): low educational attainment ($p = 0.000$; $OR = 6.767$), low skill level ($p = 0.000$; $OR = 11.364$), physical inactivity ($p = 0.007$; $OR = 4.209$), smoking ($p = 0.040$; $OR = 3.330$), diabetes mellitus ($p = 0.004$; $OR = 4.641$), hypertension ($p = 0.000$; $OR = 10.011$), obesity ($p = 0.002$; $OR = 7.103$), weight loss ($p = 0.011$; $OR = 4.485$), and COVID-19 ($p = 0.000$; $OR = 8.099$).

Among the variables in the model, a low skill level (score = 11) had the highest impact, followed by hypertension (10), COVID-19 history (8), and low educational attainment and obesity (both score = 7). Other variables scored 3-5.

The model (omnibus test $p = 0.000$) explained 82.5% of the dependent variable (Nagelkerke's R^2), correctly classified 91% of cases with 89.25% PPV, 91.79% NPV, 83% sensitivity, and 95% specificity. Calibration was good (Hosmer-Lemeshow test = 0.940) with an AUC of 0.976 (95% CI: 0.961-0.990; Fig. 2).

The resulting predictive model was composed of a global index in the form of a linear combination: $I = 11 \times x_1 + 10 \times x_2 + 8 \times x_3 + 7 \times x_4 + 7 \times x_5 + 5 \times x_6 + 4 \times x_7 + 4 \times x_8 + 3 \times x_9$, where I constitutes the proposed model; x_1 is low level of skill, x_2 is hypertension, x_3 is COVID-19, x_4 is low educational attainment, x_5 is obesity, x_6 is diabetes mellitus, x_7 is weight loss, x_8 is physical inactivity, and x_9 is smoking.

A risk score was calculated from the model for each subject, with the 70th percentile of the empirical values distribution defining two categories: low risk (under 33) and high risk (33 and over). The AUC of the scale was 0.918 (95% IC: 0.877-0.958; Fig. 3), with 90.72% PPV, 94.08% NPV, 88% sensitivity, and 95.5% specificity, indicating significant predictive value.

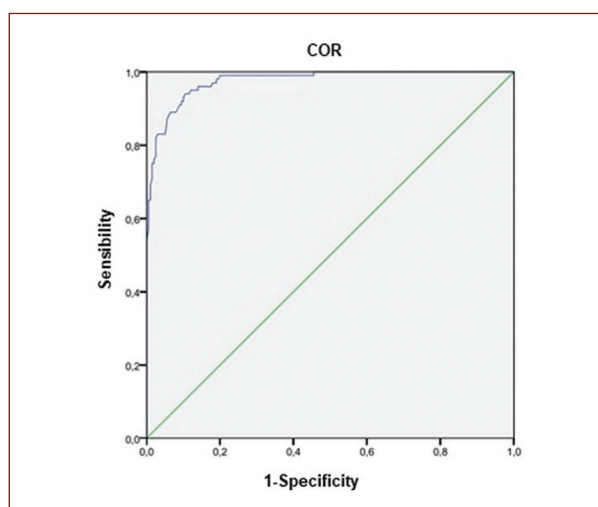
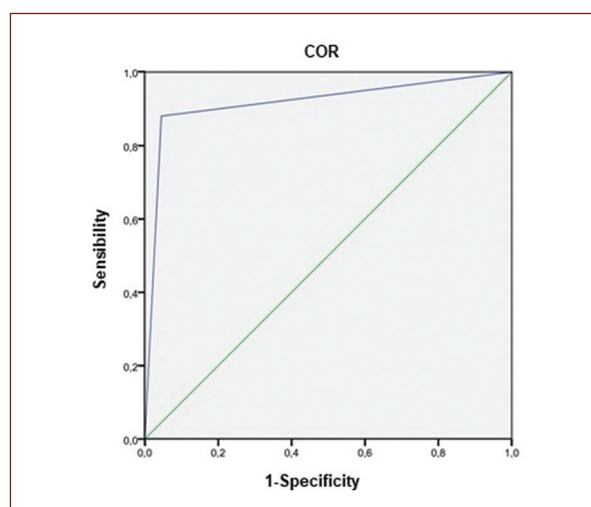
Discussion

The results of this investigation demonstrated that the predictive model can distinguish subjects with risk factors for AD who are at higher risk of mild NCD, using easily identifiable clinical and epidemiological variables, including COVID-19 history.

Table 2. Summary of multivariate binary logistic regression analysis

Variables	B coefficient	S.E.	Wald	Sig.	Exp (B)	95% CI	
						Lower limit	Upper limit
Low educational attainment	1.912	0.541	12.513	0.000	6.767	2.346	19.520
Low skill level	2.430	0.602	16.307	0.000	11.364	3.493	36.967
Physical inactivity	1.437	0.530	7.342	0.007	4.209	1.488	11.905
Smoking	1.203	0.584	4.237	0.040	3.330	1.059	10.469
Diabetes mellitus	1.535	0.527	8.472	0.004	4.641	1.651	13.048
Hypertension	2.304	0.537	18.427	0.000	10.011	3.497	28.659
Obesity	1.961	0.633	9.579	0.002	7.103	2.052	24.583
Weight loss	1.501	0.633	6.515	0.011	4.485	1.417	14.196
COVID-19	2.092	0.569	13.494	0.000	8.099	2.653	24.724

B: estimated logit coefficient; S.E.: standard error; Sig.: significance level; Exp (B): odds ratio; CI: confidence interval.

**Figure 2.** Discriminatory capacity of the model by the receiver operating curve.**Figure 3.** Discriminatory capacity of the scale by receiver operating curve.

No significant differences in sex distribution were observed between the control group and MCI patients in this study, contrasting with findings from Hernández-Ulloa et al.²⁹, whose observational study reported that women have a higher risk of cognitive decline and subsequent AD development.

In the review by Livingston et al.⁸, the percentage reduction in dementia cases was raised if several risk factors of the model of this study were intervened, thus increasing the practical contribution of the proposed model.

In the case of educational attainment, researchers⁸ have proposed that a low level should be corrected before the age of 45 to reduce cases by 5%, which represents a late intervention for the sample of this study that included adults aged over 45 years. Another investigation³⁰ suggested that the prevalence of suspected cognitive impairment presents with a higher OR as the years of education decrease.

In the review by Livingston et al.⁸, it was suggested the correction of several factors in middle age (45-65 years) causes varying degrees of reduction in

cases of dementia: physical inactivity (2%), diabetes (2%), hypertension (2%), smoking (2%), obesity (1%), among others. These factors included in the final model were described in the literature for their association with MCI and AD.

One study³¹ identified an association between physical inactivity and AD (OR 1.2; 95% CI 1.2-1.3). In a prospective cohort³², the risk of dementia increased for each 5-year decrease in the age at onset of type 2 diabetes (OR 1.24; 95% CI 1.06-1.46). One study³³ identified the highest risk of dementia in people who started smoking between 33 and 44 years of age (OR 1.42; 95% CI 0.05-3.60).

An analysis of two prospective cohorts³⁴, reported that the risk of dementia in midlife for women is higher in smokers (OR 2.63; 95% CI 1.14-6.09) and diabetics (OR 1.74; 95% CI 1.08-2.80). For men, it was higher in smokers (OR 3.19; 95% CI 1.37-7.42), diabetics (OR 2.97; 95% CI 1.50-5.89), those with low educational attainment (OR 2.93; 95% CI 1.80-4.78), with hypertension (OR 1.70; 95% CI 1.02-2.84), and low activity physical (OR 1.71; 95% CI 1.03-2.85).

A meta-analysis³⁵, identified people with untreated hypertension had a higher risk of dementia than healthy controls (OR 1.42; 95% CI 1.15-1.76), and this risk was attenuated or lost with treatment.

A systematic review and meta-analysis³⁶, identified that midlife obesity was associated with later all-cause dementia (OR 1.31; 95% CI 1.02-1.68).

Weight loss was included in the final model. One study²² revealed that participants at increased risk of AD had lost an average of 1% of their body weight per year, with no other potential causes of changes in body weight, while participants with lower risk had not experienced weight loss.

Low skill level was also included in the model. A study²⁵ concluded that people with a predominantly manual work activity have a greater risk of suffering from cognitive impairment than those who have occupations with greater intellectual requirements. Furthermore, the latter could help promote the maintenance of intact cognitive functions for longer and delay the onset of the disease.

In a systematic review and meta-analysis, it was found more than fifth of people presented with MCI (95% CI 0.17-0.28; $p < 0.001$), without meeting clinical criteria for dementia, 12 or more weeks after being diagnosed with COVID-19²⁷, that was an important factor in the sample of this study and was included in the final model.

In people aged over 65 years, a level of risk reduction was attributed to several factors, among which stands out: social isolation (5%)⁸, which in this study did not have statistical significance, but is a repeated risk factor in the literature, as well as the family history of dementia⁸, chronic kidney disease²⁰, hypercholesterolemia²¹, and ischemic heart disease²³, which did not have significant differences in this research, but its analysis is recommended in another study sample or different clinical contexts.

The model enables earlier prediction of the cognitive impairment, compared to existing models of the progression of MCI to AD focused on patients aged over 65 years, described in systematic reviews^{9,10}. Although it does not incorporate biomarkers (unlike models proposed in prior studies¹¹⁻¹³), it demonstrates significant predictive value and outperforms other MCI risk factor-based models³⁷⁻⁴⁰.

For instance:

- A Chinese MCI risk prediction system for elderly populations in China, incorporating hypertension, diabetes, educational level, hyperlipidemia, smoking, physical exercise, living alone, stroke, drinking, and heart disease, achieved an AUC of 0.859 (95% CI: 0.812-0.906, $p < 0.05$), with 86.6% sensitivity and 76.5% specificity³⁷.
- A machine learning model identifying middle-aged and older adults at high MCI risk included 13 factors (gender, education, marital status, residence, diabetes, hypertension, depression, hearing impairment, social isolation, physical activity, drinking status, body mass index, and expenditure). This model achieved an AUC of 0.774 for all incident MCI, with follow-up AUC values of 0.739, 0.747, and 0.750 at 2, 4, and 7 years, respectively³⁸.
- A risk prediction index for MCI and dementia incorporated age, female sex, years of schooling, hearing loss, depression, life satisfaction, and a number of cardio-metabolic risk factors (wide waist circumference, pre-diabetes/diabetes, hypertension, dyslipidemia). The development showed a progression AUC of 0.73, whereas the validation cohort achieved an AUC of 0.74 for MCI/dementia prevalence and incidence³⁹.
- A machine learning model for cognitive impairment in Chinese adults aged ≥ 60 years with normal baseline cognition identified four predictive features: age, instrumental activities of daily living, marital status, and baseline cognitive function. Its concordance index was 0.814 (95% CI: 0.781-0.846)⁴⁰.

A key limitation of our model is its relatively small sample size compared to the broader population with AD and mild NCD risk factors in the study context, necessitating further validation studies.

Conclusion

The predictive model of 9 variables that were easy to determine and interpret contributes to the stratification of the risk of mild NCD due to possible AD in adulthood. Therefore, it can constitute a useful tool in decision-making aimed at early and probably more effective interventions. It is recommended to validate the predictive model in cohorts with a larger estimation sample.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The 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 artificial intelligence was used in the writing of this manuscript [specify the tool and all sections of the manuscript where it was used].

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First Mexican consensus guideline for the management of IDH-mutant low-grade gliomas: Mexican guidelines for IDH-mutant gliomas

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Abstract

The objective of the study is to propose a diagnostic and therapeutic algorithm for patients with mIDH-LGG tailored to our country's healthcare setting. Patients with isocitrate dehydrogenase-mutant (mIDH) low-grade gliomas (LGGs) demand a multidisciplinary approach. Individualized management should consider local resources, patient preferences, clinical features, imaging results, and tumor pathological characteristics. We use a multidisciplinary team of neuro-oncologists, medical oncologists, neurosurgeons, radiation oncologists, neuroimaging specialists, geneticists, and neuropathologists collaborated to develop a manuscript through a Delphi consensus method. Diagnosis includes a complete clinical examination, neuroimaging, histopathological tissue examination, and molecular analysis. Treatment options include (a) surgery as the first-line approach, aiming for maximal safe resection; (b) radiation therapy, administered postoperatively or as a primary treatment in selected cases; (c) systemic therapy; and (d) palliative care for patients with advanced disease or limited therapeutic options. For asymptomatic, slow-growing tumors or elderly patients, an appropriate strategy of active surveillance might be considered. We present custom-made diagnostic and therapeutic algorithms for Mexican patients with mIDH-LGG. To optimize treatment outcomes, participation in clinical trials and early referral to specialized centers are encouraged.

Keywords: Isocitrate dehydrogenase. Low-grade glioma. Adult-type diffuse glioma.

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Primera guía de consenso mexicana para el manejo de gliomas de bajo grado con mutación IDH: guías mexicanas para gliomas con mutación IDH

Resumen

El objetivo es proponer un algoritmo diagnóstico y terapéutico para pacientes con gliomas de bajo grado IDHm adaptado al contexto del Sistema de salud Mexicano. Los pacientes con gliomas de bajo grado con mutación en la isocitrato deshidrogenasa (IDHm) requieren un enfoque multidisciplinario. El manejo individualizado debe considerar los recursos locales, las preferencias del paciente, las características clínicas, los hallazgos por imagen y las características patológicas del tumor. Se usó un equipo multidisciplinario conformado por neurooncólogos, oncólogos médicos, neurocirujanos, radiooncólogos, especialistas en neuroimagen, genetistas y neuropatólogos elaboró el presente documento mediante una metodología de consenso Delphi. El diagnóstico incluye una evaluación clínica, estudios de neuroimagen, análisis histopatológico y evaluación molecular. Las opciones terapéuticas comprenden: a) Cirugía como primera línea, con el objetivo de lograr una resección máxima segura; b) Radioterapia en el periodo postoperatorio o como tratamiento primario en casos seleccionados; c) Terapia sistémica; y d) Cuidados paliativos. En casos de tumores asintomáticos, de crecimiento lento, o en pacientes de edad avanzada, puede considerarse vigilancia activa. Se presentan algoritmos diagnósticos y terapéuticos personalizados para pacientes mexicanos con GBG-mIDH. Para optimizar los resultados del tratamiento, se recomienda la participación en ensayos clínicos y la referencia temprana a centros especializados.

Palabras clave: Isocitrato deshidrogenasa. Glioma de bajo grado. Glioma difuso del adulto.

Introduction

Primary central nervous system (CNS) tumors originate from neural and oligodendroglial cells, with gliomas being the most common type. These CNS tumors develop from cells with genetic variants that lead to tumor initiation mechanisms and are a significant cause of brain cancer-related deaths.

CNS tumors are divided according to their histological features and molecular markers as described in the 2021 World Health Organization (WHO) classification of CNS tumors¹. Primary CNS tumors are divided into six major groups: adult-type diffuse gliomas (AtDGs), pediatric-type diffuse low-grade gliomas (LGGs), pediatric-type diffuse high-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumors, and ependymal tumors. AtDGs account for most gliomas, which comprise three main distinctive types: isocitrate dehydrogenase (*IDH*)-mutated astrocytoma (mIDH astrocytoma), mIDH and 1p/19q-deleted oligodendroglioma, and *IDH* wild type (wtIDH) glioblastoma. In the WHO 2021 classification, mIDH CNS tumors fall into two main types: mIDH and 1p/19q codeleted oligodendrogliomas or mIDH astrocytomas; both are referred to in this manuscript as mIDH LGGs. Therefore, the present consensus aims to provide evidence on the epidemiology, clinical presentation, diagnosis, treatment, and prognosis of patients with mIDH LGG personalized to the current assets accessible in our country.

Methods

A multidisciplinary team of neuro-oncologists, medical oncologists, neurosurgeons, radiation oncologists, neuroimaging specialists, geneticists, and neuropathologists collaborated to develop a manuscript through a Delphi consensus method (Fig. 1), by gathering published information from our country and local accessible resources.

Epidemiology

In Mexico, a study by Hernández et al.² reported information on a cohort of 9,615 patients with CNS tumors treated at a single center for a sex proportion of 51% females and 49% males, being the neuroepithelial tumors the most prevalent (42%), followed by meningeal tumors (24%), and tumors of the sellar region (22%). Neuroepithelial tumors were supratentorial in most cases (79%). A nationwide study³ from Mexico reported that the mortality rates increased from 1.9 to 2.1/100,000 people from the years 2000 to 2017, with a male-to-female ratio of 1:2, and the age group with the highest number of deaths was in those aged 65-69 years.

Clinical presentation

In a study with information on 193 Mexican patients with CNS tumors⁴, the most common clinical presentations were headache (49%), altered mental status (32%), visual complaints (25%), seizures (21%), focal

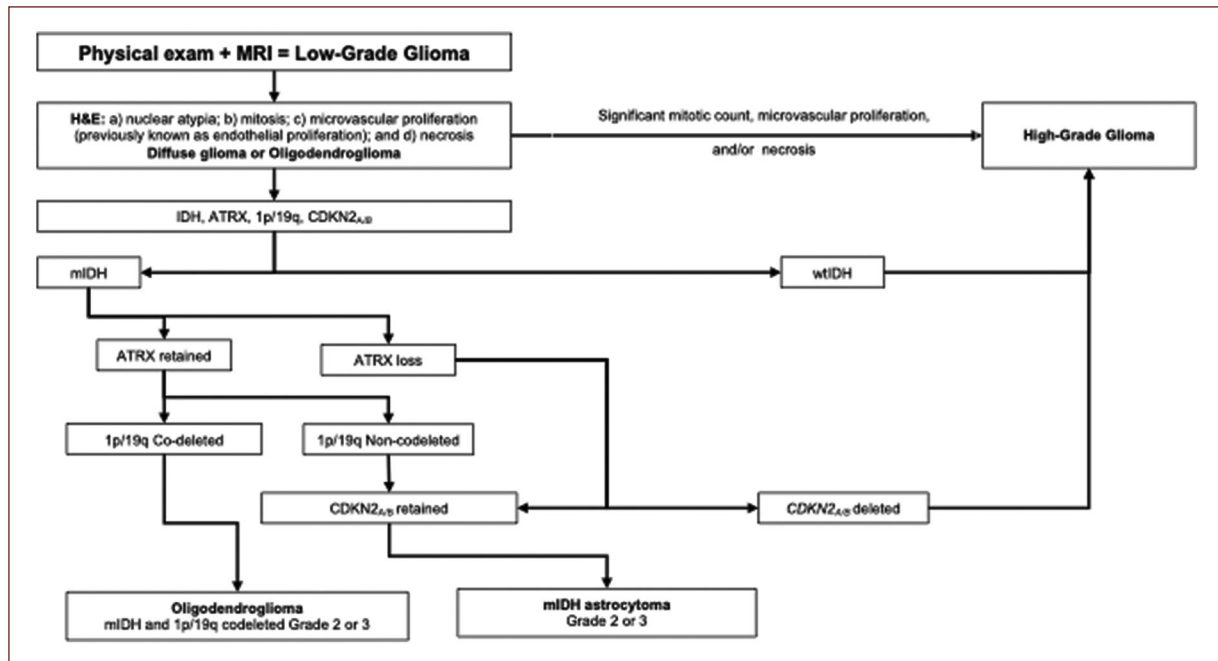


Figure 1. Diagnostic algorithm for adult patients with a suspected primary brain tumor. ATRX: X-linked mental retardation syndrome gene; CDKN: cyclin-dependent kinase inhibitor; H&E: hematoxylin and eosin; IDH: isocitrate dehydrogenase; mIDH: IDH mutated; MRI: magnetic resonance imaging; wt: wild type.

motor weakness (18%), ataxia (15%), focal sensitive complaint (8%), cognitive complaint (8%), vertigo (7%), cranial neuropathy (6%), speech disorder (5%), and abnormal movement disorder (2%).

In 30-50% of patients with CNS tumors, an epileptic seizure is the presenting clinical manifestation, and 10-30% will develop seizures later in the course of their disease⁵. LGGs with a supratentorial location have been associated with a higher risk for seizures⁶.

Clinical markers

In patients from Mexico, authors have reported that the age at presentation is significantly younger in those with gliomas and glioblastomas, with a male-to-female incidence ratio of 1.39⁷. In this population, recognized prognostic factors associated with overall survival (OS) are histological grade, Karnofsky Performance Score (KPS), resection type, chemotherapy, radiation therapy (RT), alcohol consumption, familial history of cancer, and clinical presentation⁸.

Histologic grade

The four primary histological markers traditionally used to evaluate malignancy in primary CNS tumors

are (a) nuclear atypia, (b) mitosis, (c) microvascular proliferation, and (d) necrosis. A significant mitotic count, anaplasia, high cellularity, cellular pleomorphism, and increased nuclear atypia are required to diagnose Grade 3 tumors; the presence of microvascular proliferation or necrosis is required for a CNS tumor to be considered as Grade 4⁹. According to the 2021 WHO guidelines, the histological grade should not be based solely on histological aspects and compels the use of molecular markers¹.

Molecular diagnostic markers

The main molecular markers required to classify a CNS tumor as LGG are *IDH* and 1p/19q [chromosome loss in the short arm of chromosome 1 (1p), in the large arm of chromosome 19 (19q), or both (1p/19q)].

The *IDH* biomarker should be considered the first step in the molecular classification of gliomas, followed by the 1p/19q status. A pooled analysis¹⁰ reported that patients with Grade 2 oligodendroglial tumors (mIDH and 1p/19q codeleted) had an OS of > 20 years and those with Grade 3 > 14 years. In the same study¹⁰, patients with mIDH astrocytomas classified as Grade 2 had an OS > 14 years, Grade 3 had an OS of 5-10 years, and Grade 4 around 3 years. Over 40% of Grade 2 or

3 astrocytomas and around 2% of Grade 4 astrocytomas are mIDH¹¹.

The most common *IDH* variant (mutation) in gliomas is R132H (> 70%) and can be detected by immunohistochemistry (iCH)¹²; if this IDH1 R132H is negative by iCH, sequencing of *IDH1* codon 132 and *IDH2* codon 172 should be conducted in all WHO Grade 2 and 3 diffuse astrocytic and oligodendroglial tumors, and in all patients diagnosed with glioblastoma aged < 55 years¹³.

The 1p/19q co-deletion has been associated with an improved survival rate irrespective of tumor morphology or histological Grade; it is a marker of treatment response, and its presence has also been associated with progression-free survival¹⁴.

Homozygous deletion of the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) or the cyclin-dependent kinase inhibitor 2B (*CDKN2B*) locus on 9p21 is associated with poor outcome and indicates a WHO Grade 4 disease¹. Therefore, the detection of *CDKN2A/B* is a marker of poor prognosis and excludes the diagnosis of a LGG; in other words, Grades 2, 3, or 4 gliomas should no longer be based entirely on the histological characteristics, for the presence of *CDKN2A/B* homozygous deletion results in the diagnosis of CNS WHO Grade 4, even in the absence of microvascular proliferation or necrosis.

Mutation/loss of alpha-thalassemia/mental retardation syndrome X-linked (*ATRX*) expression¹⁵ can be detected by iCH or *ATRX* sequencing. If a glioma is *ATRX* positive (mutation/loss present), it is diagnostic of an mIDH astrocytoma¹; in other words, astrocytomas are either mIDH, *ATRX* altered, and *TP53* mutated, or they are wtIDH astrocytomas.

The *BRAF* gene encodes the B-Raf protein; targetable genetic variants in *BRAF* have been detected in 15 to 20% of LGGs, and their prognostic and therapeutic significance is under study¹⁶⁻¹⁸. Finally, the WHO has never implemented the use of Ki-67 antibodies to assess the degree of malignancy, so we do not endorse using this marker to establish a diagnosis or guide therapeutic interventions.

Molecular tests – Summary

- Detection of mIDH and *ATRX* by iCH tests should be performed routinely for all gliomas. If negative, IDH1 codon 132 and IDH2 codon 172 sequencing should be determined in all WHO Grade 2 or 3 gliomas and patients with glioblastoma if the age at diagnosis was < 55 years. A 1p/19 codeletion status should be

determined in all mIDH gliomas. *CDKN2A/B* deletions should be investigated in all mIDH astrocytomas.

- The suffix NOS is used when insufficient DNA is found, and the suffix NEC when molecular studies are done but the results do not fit the WHO diagnostic criteria.

Diagnosis

The diagnosis of a CNS tumor is often made in a previously healthy patient who presents with focal neurological deficits such as focal motor weakness, new-onset seizures, and headache. Patients may also be diagnosed incidentally through neuroimaging findings. If a glioma is suspected, we recommend a diagnostic algorithm described in [figure 2](#).

Magnetic resonance imaging (MRI)

The proposed imaging protocol includes the following¹⁹:

- Axial fluid attenuation inversion recovery (FLAIR) with canthomeatal alignment: 3-5 mm sections, 1 mm interslice gaps, slice registration preserved as much as possible between sequential studies.
- Axial T2: 5 mm sections, 1 mm interslice gap.
- Coronal T1: 5 mm sections, 1 mm interslice gap.
- Post-gadolinium chelate (contrast agent as per local clinical practice): coronal T1, axial T1.
- Alternatively, pre-gadolinium and post-gadolinium volumetric T1 may replace axial and coronal T1-weighted sequences.
- Supplementary imaging methods that can be done at some specialized centers include two-dimensional or three-dimensional spectroscopic imaging (MR spectroscopy), perfusion imaging (DSC-MRI), and diffusion-weighted imaging (–B = 0, B = 1000).

Positron emission tomography (PET) imaging

¹¹C-methionine (¹¹C-MET) and ¹⁸F-fluoroethyltyrosine (¹⁸F-FET) tracer PET might be used by intravenous administration; ideally 6 mm or better spatial resolution is recommended. Glucose metabolism in LGGs is decreased compared to that of a normal brain; ergo, ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET is currently considered to be of limited use. Compared with ¹⁸F-FDG, the uptake of amino acids (¹¹C-MET and ¹⁸F-FET) is less affected by inflammatory processes, although tumor specificity is not perfect²⁰. The addition of

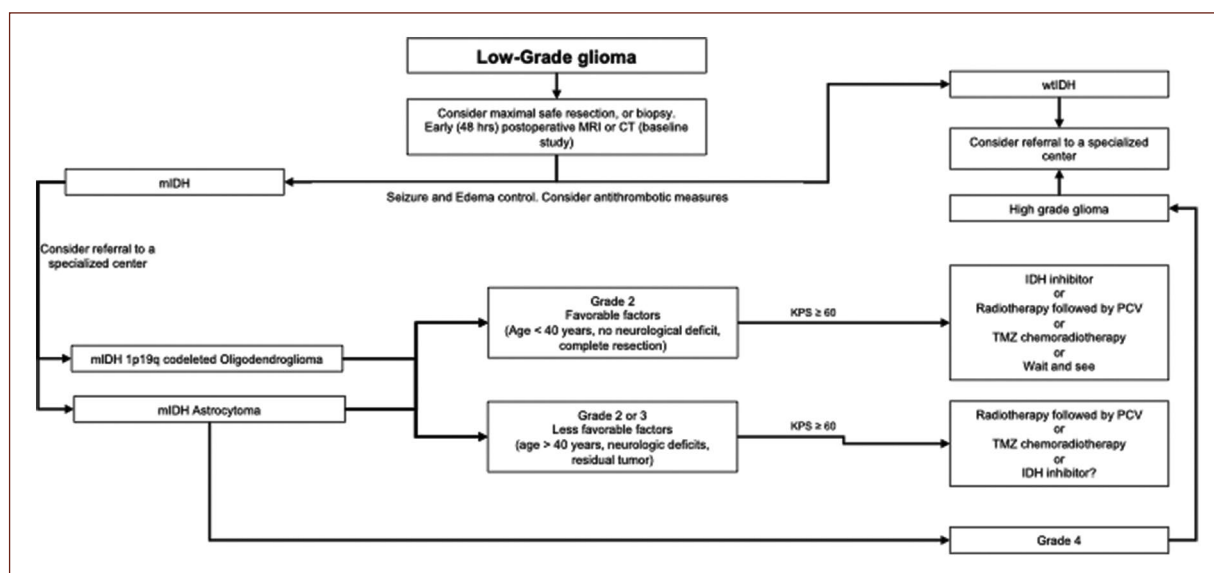


Figure 2. Therapeutic algorithm for adult patients with mIDH low-grade glioma. IDH: isocitrate dehydrogenase; mIDH: IDH mutated; KPS: Karnofsky performance status; MRI: magnetic resonance imaging; PCV: procarbazine, lomustine (CCNU), and vincristine; TMZ: temozolomide; wtIDH: IDH wild type.

^{18}F -FET PET to MRI has been shown to improve the diagnosis of active gliomas by increasing the specificity from 53% to 94%, with unchanged sensitivity (93-96%) in one study²¹. ^{11}C -MET PET is well suited to follow the effects of RT, and it enables the differentiation of recurrent tumors from radiation necrosis²²⁻²⁴.

Treatment

The CNS WHO grade¹ has traditionally been used to guide therapeutic interventions. Younger age and better performance status at diagnosis are the major prognostic factors associated with longer survival²⁵.

Surgical therapy

The first line of treatment in patients with LGGs is to consider a maximal safe resection (MSR), which means resecting as much of the tumor as possible. An MSR is associated with longer OS and progression-free survival (PFS) and helps achieve an onco-functional balance and improve the quality of life (QoL). Several techniques and tools have been used to achieve this onco-functional balance, including navigation, functional MRI, intraoperative MRI, ultrasonography, fluorescence-based visualization with 5-aminolevulinic acid (5-ALA)²⁶, and functional monitoring, all of which are encouraged in the operating room²⁷. Surgical

resection must be personalized, for no “standard” surgical approach exists²⁸.

Gross total resection (GTR) has been defined as the absence of residual lesion, based on T1-weighted contrast enhancement (CE) images; subtotal resection (STR) was considered when tumoral tissue was left in the surgical field, even if no tumor is seen in the post-operative MRI, STR was also considered in the presence of residual tumor after an extent of resection (EOR) of > 90%; partial resection (PR) was defined as the presence of > 10% but < 90% EOR²⁹; finally, a supratotal resection (SpTR) was considered when the resection involved the removal of more than 100% of the visible tumor tissue, true SpTR was defined as excision past all discernible and visible MRI abnormalities, including fluid-attenuated inversion recovery (FLAIR) borders^{30,31}. In 2023, the Response Assessment in Neuro-Oncology (RANO) resect group³² stratified the EOR into four categories as presented in table 1. The EOR is a prognostic factor; thus, efforts to obtain a Class 1 or 2 resection are recommended.

After surgery, a watch-and-wait approach is advised for younger patients (< 40 years) who have achieved maximal CE resection and for those younger patients with submaximal CE resection if there is no neurologic deficit beyond symptomatic epilepsy³³; with this approach, studies have estimated OS rates of 99% at 2 years and 93% at 5 years; and PFS rates of 82% at 2 years and 48% at 5 years²⁹.

Table 1. RANO resect group categories for the extent of resection

Class 1 Supramaximal CE resection	Class 2 Maximal CE resection		Class 3 Submaximal CE resection		Class 4 Biopsy
0 cm ³ CE + ≤ 5cm ³ nCE	Class 2A Complete CE resection	Class 2B Near-total CE resection	Class 3A Subtotal CE resection	Class 3B Subtotal CE resection	No reduction of tumor volumen
	0 cm ³ CE + < 5cm ³ nCE	≤ 1 cm ³ CE	≤ 5cm ³ CE	> 5cm ³ CE	

Supramaximal resection of CE tumor = beyond CE tumor borders (cut-off values remain to be defined); *complete resection* of CE tumor = removal of all CE tumor; *near total resection* of CE tumor = 95-99.9% CE tumor reduction + ≤ 1 cm³ residual CE tumor; *subtotal resection* of CE tumor = 80-94.9% CE tumor reduction + ≤ 5 cm³ residual CE tumor; *partial resection* of CE tumor = 5 cm³ residual CE tumor (administered for mass effect-related symptoms); or *biopsy* = no tumor reduction (intervention done for tissue-based diagnosis only).
CE: contrast enhanced; nCE: non-contrast enhanced.

Radiotherapy

RT aims to improve local control, increase OS, prevent or delay malignant transformation, minimize treatment-associated adverse events, and maintain or improve patients' QoL. A radiation oncology specialist should always supervise the dose, timing, and scheduling of RT.

Early administration of RT has been demonstrated to prolong PFS and improve seizure control³⁴. Deferring RT until disease progression can be considered for those with LGGs, aged < 40 years, and GTR²⁹. In patients without these conditions or symptomatic LGGs (i.e., seizures), post-operative (3-6 weeks after surgery)^{35,36} RT should be considered, with an optimal dose of 50-60 Gy in 1.8-2.0 Gy per fraction^{37,38}. Hypofractionated radiotherapy with a higher dose per fraction and a lower total dose might be appropriate for older (> 65 years of age) and those with poor performance status (KPS < 70).

Systemic treatment

Before considering any systemic treatment, a complete blood count and hepatic/renal function tests should be determined. The addition of adjuvant PCV (procarbazine, lomustine [CCNU], and vincristine) to post-operative RT in patients with high-risk LGGs (pre-operative tumor diameter ≥ 4 cm or greater, astrocytoma/oligoastrocytoma histologic type, and/or residual tumor ≥ 1 cm) resulted in an increased OS (13.3 years vs. 7.8 years) and longer PFS (4.0 years vs. 10.4 years, $p < 0.001$)³⁹.

At present, the standard of care for patients with LGGs considered candidates for post-operative therapy is RT, followed by PCV chemotherapy³⁹. Studies have shown the benefit of adding PCV chemotherapy in

patients with oligodendrogliomas³³. The median OS (MOS) times varied significantly, being 1.9 years for those with wtIDH tumors, 6.9 years for mIDH/1p19q non-codeleted tumors, and 13.9 years for mIDH/1p19q co-deleted tumors. Interestingly, the mIDH subgroups (1p19q co-deleted or non-codeleted) demonstrated longer survival with the addition of PCV; mIDH/1p19q non-codeleted tumors improved their MOS from 4.3 years to 11.4 years (hazard ratio [HR] = 0.38, $p = 0.01$), and those with mIDH/1p19q codeleted tumors from 13.9 years to still not reached (HR = 0.21, $p = 0.04$). In contrast, the wtIDH group did not experience a survival benefit from receiving PCV.

Promising outcomes have been observed with combined temozolomide (TMZ) and RT for patients with high-risk LGG. The phase II single-arm study, RTOG 0424, enrolled 136 patients diagnosed with WHO Grade 2 gliomas. Eligibility criteria included at least three unfavorable factors: age ≥ 40 years, pre-operative tumor diameter ≥ 6 cm, bi-hemispheric tumor, astrocytoma histology, and/or pre-operative neurological function status > 1. Patients received 54 Gy in 1.8 Gy fractions with concurrent and adjuvant TMZ for up to 12 cycles. The observed 3-year OS rate of 73.5% significantly exceeded prespecified historical control values ($p < 0.001$)⁴⁰.

Adjuvant TMZ has also been shown to improve survival compared to RT alone for patients with non-1p/19q codeleted WHO Grade 3 gliomas. The CATNON (EORTC 26053-22054) phase III trial randomized 745 patients with non-codeleted WHO Grade 3 gliomas to receive RT (total 59.4 Gy in 1.8 Gy per fraction) with or without adjuvant TMZ (12 4-week cycles) or to receive RT plus concurrent TMZ with or without adjuvant TMZ. With a median follow-up of 55.7 months, adjuvant TMZ improved survival compared with no

adjuvant treatment (MOS 82.3 months vs. 46.9 months; HR = 0.64, $p < 0.001$).

Exploratory analysis revealed that patients with mIDH, 1p/19q non-codeleted tumors had a longer PFS when treated with RT alone compared to TMZ alone (HR = 1.86, $p = 0.004$)⁴¹. Considering this data, TMZ as monotherapy could be considered if RT cannot be administered⁴².

Temozolomide (TMZ)

TMZ is an oral DNA alkylating agent that penetrates the blood-brain barrier and is the most common agent used in glioma treatment³⁶. The chemoradiation therapy, also known as the Stupp regimen, consists of concurrent and adjuvant TMZ. Concomitant chemotherapy consists of TMZ at a dose of 75 mg per square meter per day (mg/m²/d), given 7 days per week from the 1st day of radiotherapy until the last day, but not longer than 49 days. After a 4-week break, patients are then to receive up to six to twelve cycles of adjuvant TMZ at a dose of 150 to 200 mg/m²/d for 5 days scheduled every 28 days (days 1-5 with TMZ and days 6-28 without TMZ = 1 cycle). Hematologic toxic effects should be followed, and TMZ might cause lymphopenia and thrombocytopenia. Pneumocystis jirovecii pneumonia prophylaxis should be considered. A retrospective study of antiemetic therapy with ondansetron, ondansetron + domperidone, and ondansetron + olanzapine showed that the latter is the better option⁴³.

Procarbazine, lomustine (CCNU), and vincristine [PCV]

The first clinical trial to demonstrate an increase in OS with the addition of adjuvant chemotherapy (post-radiation chemotherapy) in 251 patients with high-risk LGGs, defined as age > 40 years or subtotal resection/biopsy, was the RTOG 9802³⁹. Chemotherapy consisted of 6 cycles of procarbazine (at a dose of 60 mg per square meter of body-surface area orally per day on days 8 through 21 of each cycle), CCNU (at a dose of 110 mg per square meter orally on day 1 of each cycle), and vincristine (at a dose of 1.4 mg per square meter [maximum dose, 2.0 mg] administered intravenously on days 8 and 29 of each cycle). The cycle length was 8 weeks. Patients who received RT plus PCV had a longer median OS than those who received RT alone (13.3 vs. 7.8 years); the HR for death was 0.59 ($p = 0.003$). The ten-year PFS was 51% in the PCV and radiation group vs. 21% in the RT alone group; the OS

rates at 10 years were 60% and 40%, respectively. A *post hoc* analysis³³ determined that treatment with post-radiation chemotherapy with PCV was associated with longer PFS [HR = 0.22 (95% confidence interval [CI]: 0.11-0.40), $p = 0.003$] and OS [HR = 0.18 (0.09-0.40)]. In contrast, no significant difference in either PFS or OS was observed with the addition of PCV in patients in the wtIDH group. Unfortunately, the access to PCV in Mexico is limited.

Vorasidenib

In a double-blind, randomized, placebo-controlled, phase 3 trial, 331 patients with Grade 2 mIDH oligodendroglioma or astrocytoma, with confirmed *IDH1* and *IDH2* mutations, received 40 mg of vorasidenib or placebo, once daily, orally in continuous 28-day cycles⁴⁴. The median PFS in the vorasidenib group was 27.7 vs. 11.1 months; the HR for disease progression or death was 0.39 (95%CI 0.27-0.56), $p < 0.0001$. A Grade 3 or higher adverse event occurred in 9.6% of the treatment group vs. 0 in the placebo group. Vorasidenib has now been approved for patients with mIDH LGGs.

Palliative care

It is essential to consider palliative care for patients with poor performance (KPS < 60). Palliative care offers a comprehensive approach to improving a patient's quality of life by addressing their physical, psychological, and emotional needs and can provide additional support that complements medical treatment. Integrating palliative care into the care plan can help optimize a patient's well-being and provide support throughout their illness⁴⁵.

Monitoring and follow-up

Watch-and-wait strategies might be appropriate in patients with Grade 2 tumors, especially if asymptomatic or with a GTR. In addition to clinical examination, MRI is the standard diagnostic measure for evaluating disease status or response; using the RANO criteria, clinicians should be able to assess every 3 months if the patient has a complete response, partial response, stable disease, or progression^{19,46}. A brain MRI should be performed every 3-6 months for five years, then at least every 6 months.

The following definitions described in [table 2](#) should be universally included in each MRI report essential

Table 2. The Response Assessment in Neuro-Oncology (RANO) for gliomas

Complete response	Partial response	Stable disease	Progression
Disappearance of all measurable and non-measurable disease in T1 + GAD	≥ 50% decrease in sustained injury over 4 weeks at T1 + GAD	Not eligible for complete, partial response, or progression in T1 + GAD	≥ 25% increase in T1 + GAD enhanced lesions or any new lesions
Lesions that do not enhance in T2/FLAIR	Stable or non-enhancing lesions in T2/FLAIR	Stable lesions that do not enhance in T2/FLAIR	Significant increase in T2/FLAIR injury
No use of corticosteroids	With the same or lower dose of corticosteroids	With the same or lower dose of corticosteroids	Increased dose of corticosteroids
Clinically stable or improving	Clinically stable or improving	Clinically stable or with new symptoms	Clear clinical deterioration
Patients with non-measurable disease cannot have a complete response	Patients with non-measurable disease cannot have a partial response	Better response in patients with non-measurable disease	Clear progression of the disease not measurable

GAD: gadolinium; FLAIR: fluid-attenuated inversion recovery.

factors to ensure that the recommendations are both practical and achievable.

Conclusion

mIDH LGGs represent a significant proportion of primary CNS tumors. We have reviewed their clinical implications and management and presented recommendations based on the available resources. We emphasize a multidisciplinary approach when managing every patient with a LGG.

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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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Human rabies: autopsy case

Rabia humana: caso de autopsia

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Etiology

The rabies virus belongs to the genus Lyssavirus, family Rhabdoviridae, and is bullet-shaped¹.

Mr. Editor:

We present the case of a 13-year-old boy living in a rural area with poor hygiene and overcrowding. His illness began on April 3, while he was working in the field. He experienced paresthesias in both lower extremities, which progressed to the upper extremities, and urinary retention. He was evaluated on April 5; family members reported that last February. He had suffered injuries consistent with bat bites on his right toes.

Post-exposure rabies prophylaxis was initiated due to the severe risk of a bat bite with suspicious symptoms. Human rabies immunoglobulin (HRIG) and the first dose of human rabies vaccine were administered. The corresponding epidemiological study was carried out, and the health jurisdiction was notified.

The case was referred to the Eva Samano de Lopez Mateos Children's Hospital in Morelia, Michoacan, on April 7, where his condition worsened with sialorrhea, confusion, vomiting, fever, photophobia, and respiratory distress with oxygen desaturation of 83%.

On April 8, 2024, at 11:35 a.m., the patient presented with cardiorespiratory failure, and resuscitation efforts were initiated. Death was declared at 11:50 a.m. On the same day, an autopsy was requested from the pathology service of the "Dr. Miguel Silva" Civil Hospital, where the brain was removed.

According to the epidemiological protocol, the Institute of Diagnosis and Epidemiological Reference requested a cerebral hemisphere to perform immunofluorescence tests. The right cerebral hemisphere and the left cerebellar hemisphere were analyzed in the pathology department of the "Dr. Miguel Silva" Civil Hospital (Fig. 1).

Eosinophilic inclusions were found in the cytoplasm of neuronal cell bodies in the midbrain, hippocampus, and cerebellum, as well as neuronal cell bodies with loss of nuclei (degenerated neurons), Virchow-Robbin spaces with perivascular lymphocytic infiltrate, known as "perivascular cuffs," and neuropil edema (Fig. 2).

These histological findings confirmed the diagnosis of rabies meningoencephalitis.

Discussion

In 2019, the World Health Organization awarded Mexico the certificate of the first country free of human rabies, transmitted by dog bites; However, this has created confusion, creating a false sense of rabies "eradication," while ignoring the consequences of infection through other vectors, such as bat bites.

Rabies virus is the most important virus in the genus *Lyssavirus* because, from a global perspective, its distribution, human cases (> 55,000 deaths/year), wide range of potential reservoirs, and veterinary and economic cost implications make it the most important viral zoonosis. Rabies is thought to have occurred in tropical America since pre-Hispanic times, being transmitted

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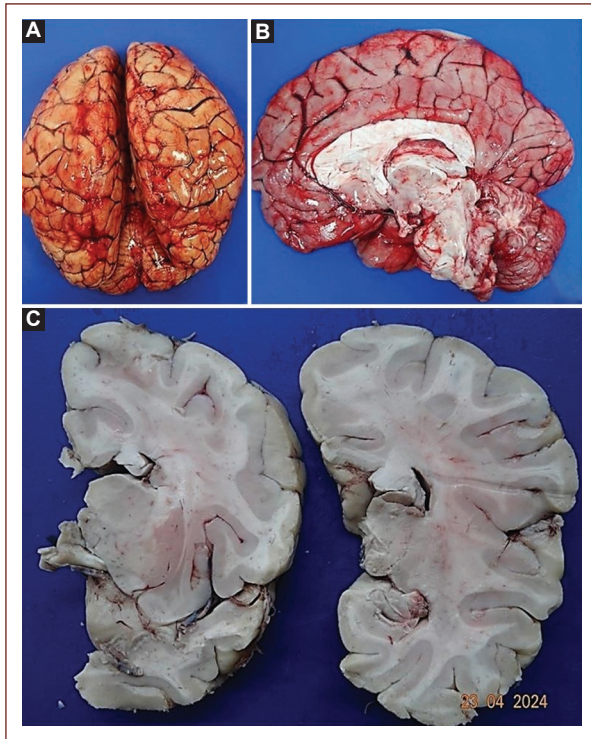


Figure 1. **A:** dorsal view of the brain. **B:** sagittal view of the brain; both show severe edema and congestion of the leptomeninges. **C:** coronal sections showed cortical congestion.

predominantly by hematophagous vampire bats, although recent phylogenetic reconstructions suggest that the rabies virus in the Americas is unlikely to have originated from vampire bats¹.

The vampire bat (*Desmodus rotundus*) is both host and vector of the rabies virus. In contrast, the other two hematophagous species (*Diphylla ecaudata* and *Diademus youngii*) are not considered important transmitters of the virus. It is important to mention that cases of rabies in non-hematophagous bat species in Mexico are very rare, and do not represent a risk of transmission to humans¹.

Diagnostic

To confirm the diagnosis of human rabies meningoencephalitis, premortem (in life) or postmortem can be performed².

Corneal

A slide is firmly pressed against the central part of the cornea and repeated twice in each eye. The slides

are fixed in acetone. This test is insensitive and sometimes traumatic².

Saliva

Collect saliva from the floor of the mouth using a dropper or syringe and place it into a screw-capped test tube containing 2 mL of saline solution. Send the sample immediately to the laboratory and store it at a temperature of 4-8 °C. Saliva inducers should not be used, as they may interfere with viral replication².

Skin biopsy

A skin sample measuring 10 mm in diameter is taken from the nape of the neck, at the level of the hairline, including the dermis (hair follicles). It is placed in a test tube (with a screw cap) containing 2 mL of saline or 50% glycerol in saline. It is identified, packaged, and kept refrigerated².

Serum and cerebrospinal fluid (CSF)

They are obtained 10 days after the onset of neurological symptoms. Detection of antibodies in serum is only useful in unvaccinated patients; this limitation does not apply to CSF. The required amount for each sample is 2 mL. This test is less sensitive than others, as in a minority of cases it may show the typical changes of viral meningoencephalitis².

Postmortem diagnosis

It is performed by extracting the brain and taking a sample to look for Negri bodies, lymphocytic infiltration in Virchow-Robin spaces, eosinophilic degeneration of the cytoplasm, and nuclear effacement².

Immunofluorescence

It is based on the detection of antigens for the rabies virus, and is the gold standard².

Differential diagnosis

The diagnosis of human rabies is usually suggested by epidemiologic and clinical findings and confirmed in the laboratory. The diagnosis is not difficult if there is a history of animal bite exposure and if a full spectrum of symptoms and signs has appeared. Otherwise,

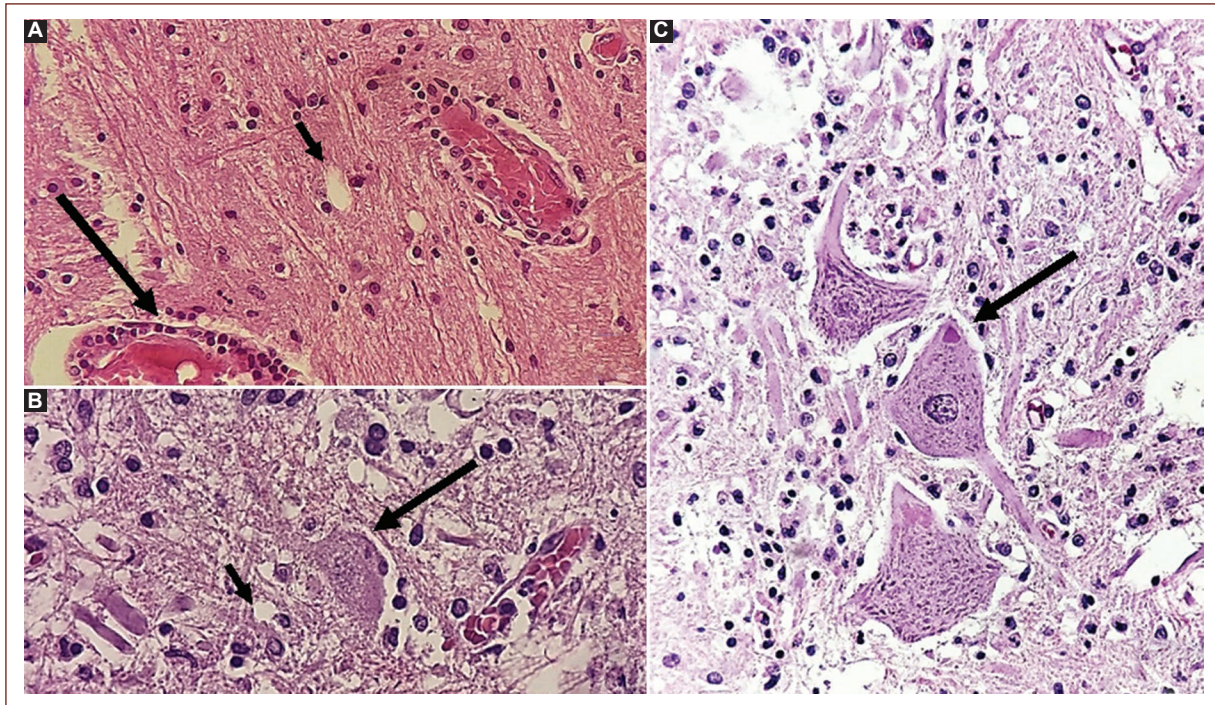


Figure 2. **A:** brain parenchyma with perivascular lymphocytic infiltrate (cuffs) (long arrow), and neuropil vacuolation (short arrow) in relation to edema. H&E, $\times 400$. **B:** hippocampus section, degenerated neuron (long arrow), and intense neuropil vacuolation (short arrows). H&E, $\times 400$. **C:** cerebellum, three Purkinje cells with different degrees of degeneration; the central neuron showed an eosinophilic cytoplasmic inclusion, Negri body (arrow).

careful but rapid assessment of the epidemiologic and clinical features of less typical cases is essential before special laboratory tests are performed. Every patient with neurologic signs or symptoms or unexplained encephalitis should be questioned about the possibility of animal exposure in a rabies-endemic area inside or outside the country of residence³.

Early in the course of illness, rabies can mimic numerous infectious and non-infectious diseases. Many other encephalitides, such as those caused by herpesviruses and arboviruses, resemble rabies. Other infectious diseases also may resemble rabies, such as tetanus, cerebral malaria, rickettsial diseases, and typhoid. Paralytic infectious illnesses that may be confused with rabies include poliomyelitis, botulism, and simian herpes type B encephalitis³.

Non-infectious diseases that may be confused with rabies encompass a number of neurologic syndromes, especially acute inflammatory polyneuropathy (Guillain-Barré syndrome), as well as allergic post-vaccinal encephalomyelitis secondary to vaccination with nervous-tissue rabies vaccines, intoxication with poisons

or drugs, withdrawal from alcohol, acute porphyria, and rabies hysteria. Guillain-Barré syndrome may be mistaken for the paralytic form of rabies, and vice versa³.

Post-exposure prophylaxis

All persons exposed to rabies should start by thoroughly washing and cleaning out the wound with soap and water or a virucidal agent. This should be followed immediately by passive rabies immunization with rabies immune globulin (RIG) in unvaccinated patients and vaccination with a cell culture rabies vaccine⁴.

Equine rabies immunoglobulin may also be used as an alternative if HRIG is not available⁴.

Unvaccinated individuals should receive four 1-mL dose vaccines and RIG promptly after being exposed to the rabies virus⁴.

The first dose of the vaccine should be administered as soon as possible after the exposure, on what is considered day 0. It can also be started weeks to months after exposure within the incubation period if signs and

symptoms of rabies have not yet appeared. The next three doses should then be administered on days 3, 7, and 14 after the first vaccination⁴.

In our case, the consequences of the bat bite were not known, so medical attention was sought only when the patient already presented irreversible clinical symptoms. Due to the late complexity of the symptoms, no prior premortem diagnosis was performed.

The diagnosis was confirmed postmortem by immunofluorescence in the brain and histologically with brain sections.

Conclusion

The case of a 13-year-old boy who developed rapid encephalomyelitis of approximately 6 weeks duration is presented. He was not treated in time because he did not receive medical attention; therefore, the diagnosis was not timely. In this case, the prolonged progression is notable, as the fatality rate of the disease is typically within the 1st week after the bite.

In 2019, Mexico was certified as the first country in the world to eliminate human rabies transmitted by dog bites. However, the cases reported in recent years have been caused by bat bites.

The population should be advised on how to act when there is certain or suspected evidence of a bite from a rabies carrier, and how to take the necessary health measures, because the window of opportunity is very short and is essential for a good prognosis, as the outcome is often fatal.

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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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