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EDITORIAL

Contemporary neurology: controversies, economic impact, and innovation

Neurología contemporánea: controversias, impacto económico e innovación

Raúl Medina-Rioja[1,2]* *and Carlos Arellano-González*[3]

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The impact of medical advances extends beyond clinical decision-making. This is particularly evident when such progress carries legal or economic implications for society. In this regard, the present issue of the *Revista Mexicana de Neurociencia* (RMN) brings together several original articles addressing topics, such as brain death, organ donation, and the economic impact of stroke treatment. It also includes a relevant review on the multiple manifestations of dementia or cognitive impairment, along with a novel proposal for the assessment of dyspraxia, thus composing a diverse and highly engaging issue.

In the article by Castillo-Sánchez-Lara et al., the authors explore the pilot design of a scale aimed at providing a comprehensive assessment of dyspraxia, including its different subtypes (visual, constructive, among others). Its main strengths include the sample size (200 patients), appropriate anatomoclinical correlation, and a solid level of statistical confidence, laying the groundwork for larger studies and future validation processes.

Yeverino-Gutiérrez et al. present an analysis of attitudes toward organ donation among populations in northern Mexico, demonstrating – contrary to popular belief – that a high percentage of respondents would be willing to become organ donors if needed.

Múnera-Libreros et al., describe a cohort of 74 patients diagnosed with Duchenne muscular dystrophy, analyzing variables, such as survival, molecular diagnosis, and interventions performed. This work highlights the complexity of genetic diseases and the need to deepen our understanding to achieve effective treatments.

Estrada-Matos et al. present an analysis that confirms a widely accepted clinical notion: timely treatment of ischemic stroke, regardless of the therapeutic modality, is associated with a lower long-term economic impact compared with persistent disability. This finding underscores the importance of implementing strategies, such as thrombolysis, even in resource-limited centers.

In the realm of controversial topics, Machado et al. emphasize the need for ancillary studies in the diagnosis of brain death in patients with posterior fossa lesions, due to the inherent limitations of clinical evaluation in this context.

Finally, Pérez-García et al. present a narrative review of the multiple manifestations of dementia, addressing fundamental aspects, such as risk factors, epidemiology, and clinical features, constituting a valuable resource for physicians beginning their training in neurodegenerative diseases.

Taken together, the articles in this issue of the RMN address highly relevant clinical and conceptual domains, several of which carry important practical and ethical implications, and will undoubtedly be of great interest to readers.

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ORIGINAL ARTICLE

Clinical and epidemiological profile of patients with Duchenne muscular dystrophy in a tertiary care pediatric hospital in Mexico

Rosa H. Múnera-Libreros[1], *Matilde Ruiz-García*[2], *and Jorge Sanchez-Vargas*[3]*

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Abstract

Objective: *The objective of the study is to describe the clinical, epidemiological, and genetic profile of patients with Duchenne muscular dystrophy (DMD) treated at a tertiary care pediatric hospital in Mexico.* **Methods:** *This was a retrospective, observational study of 74 patients with genetically or biopsy-confirmed DMD who were evaluated by Pediatric Neurology between 2010 and 2022. Clinical, demographic, biochemical, genetic, and therapeutic data were analyzed using descriptive statistics.* **Results***: All patients were male. The median age of symptom onset was 3 years, with a median age at diagnosis of 7 years. At the initial evaluation, 87% were in the ambulatory stage. Gastrocnemius hypertrophy (94.5%) and Gowers' sign (87.8%) were common findings. Deletions in exons 45-55 of the DMD gene were identified in 74% of molecularly confirmed cases. Steroid therapy was administered to 81% of patients, mostly deflazacort. Neuropsychiatric (41.9%), orthopedic (44.5%), and respiratory (44.6%) comorbidities were frequently observed. Only 6.7% were candidates for gene therapy. The mean age at loss of ambulation was 10.2 years; one death due to respiratory failure was recorded.* **Conclusions:** *Despite advances in diagnostic and therapeutic strategies, patients with DMD in this setting continue to have poor outcomes, likely due to low clinical suspicion leading to delayed diagnosis and treatment. Early detection protocols, measurement of creatine kinase in children with motor delays, and multidisciplinary management are crucial to improving outcomes and survival.*

Keywords: *Duchenne muscular dystrophy. Molecular testing.*

Perfil clínico y epidemiológico de pacientes con distrofia muscular de Duchenne en un hospital pediátrico de tercer nivel de atención en México

Resumen

Objetivo: *Describir el perfil clínico, epidemiológico y genético de pacientes con distrofia muscular de Duchenne (DMD) atendidos en un hospital pediátrico de tercer nivel en México.* **Métodos:** *Estudio observacional, retrospectivo, de una cohorte de 74 pacientes con diagnóstico confirmado de DMD, atendidos entre 2010 y 2022 por Neurología Pediátrica. Se analizaron variables clínicas, demográficas, bioquímicas, genéticas y terapéuticas mediante estadística descriptiva.* **Resultados:** *Todos los pacientes fueron varones. La edad mediana de inicio de síntomas fue de 3 años, con diagnóstico neurológico a los 7 años. En 87% de los casos, la valoración inicial fue en fase ambulatoria. El 94.5% presentó hipertrofia de gastrocnemios y el 87.8% signo de Gowers. Se identificaron deleciones en los exones 45-55 del gen DMD en 74% de los casos confirmados genéticamente. El 81% recibió esteroides, principalmente Deflazacort. Se observaron comorbilidades neuropsiquiátricas (41.9%),*

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ortopédicas (44.5%) y respiratorias (44.6%). Solo 6.7% fue candidato a terapia génica. La edad media de pérdida de la marcha fue 10.2 años; se reportó una defunción. **Conclusiones:** *El diagnóstico y tratamiento de la DMD continúa siendo tardío en México. La implementación de protocolos de detección temprana, evaluación con CPK ante retraso motor, y un enfoque multidisciplinario podrían mejorar la calidad de vida y la supervivencia en esta población.*

Palabras clave: *Distrofia muscular de Duchenne. Pruebas moleculares.*

Introduction

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy in childhood. It belongs to the group of dystrophinopathies, follows an X-linked recessive inheritance pattern, and affects approximately 1 in every 5,000-6,000 live male births.[1]

Dystrophin is the largest gene identified in humans and, as a result, is highly susceptible to spontaneous mutations;[2] this protein plays a crucial role in the production and stabilization of muscle membrane proteins. The absence of dystrophin leads to progressive destruction of muscle fibers, which are subsequently replaced by connective and adipose tissue.[3]

In Mexico, dystrophinopathies, particularly DMD and Becker muscular dystrophy (BMD) muscular dystrophies, represent the most common types of muscular dystrophy, with an estimated prevalence of 4.78/100,000 individuals and a frequency of 1 in 3,500-5,000 live male births. In a recent study of 169 Mexican patients, 68% were found to have pathogenic variants associated with dystrophinopathies, with DMD/BMD being the most frequent, emphasizing the substantial burden of these conditions in the country. Moreover, an analysis of 72 male patients with a clinical suspicion of muscular dystrophy showed that 68% had genotypes related to dystrophinopathies.[4,5]

DMD should be suspected in boys aged 2-4 years who present with delayed motor milestones as the initial manifestation, subsequently developing motor clumsiness, muscle weakness, difficulty climbing stairs, calf hypertrophy, toe-walking, and Gowers' sign.[6] In these cases, creatine kinase (CK) levels must be measured and are typically elevated 10-100 fold above the normal range (20-200 IU/L).[7] Diagnostic confirmation is achieved through genetic testing;[6] however, if genetic testing is negative and clinical suspicion persists, a muscle biopsy with immunohistochemistry for dystrophin should be considered.[8] The frequency of clinical manifestations at the initial evaluation is summarized in table 1.

Delayed diagnosis negatively impacts quality of life.[1] At present, there is no definitive cure for DMD, making a timely and accurate diagnosis essential for optimal patient management.[9] Early diagnosis and care focused on preserving muscle strength, as well as preventing and treating cardiac, respiratory, and orthopedic complications, significantly influence patients' quality of life and survival.[10,11] To date, the only pharmacologic treatments shown to reduce disease progression are glucocorticoids; gene therapy is reserved for patients with specific mutations and is therefore only applicable to a select group of patients.[12]

Although systematic reviews have been published, the heterogeneity found across different outcomes and populations is high, underscoring the need for new epidemiological evidence due to the lack of high-quality studies.[13]

The objective of this study is to describe the clinical, epidemiological, and genetic profile of DMD patients treated at a tertiary care institute in Mexico and to determine the clinical stage of the disease at the time of first neurology evaluation.

Materials and methods

This was an observational, longitudinal, retrospective study including a series of 74 patients under 18 years of age with a molecular or muscle biopsy-confirmed diagnosis of DMD, who were evaluated by the Pediatric Neurology service over a 12-year period (2010-2022) at a tertiary care center in Mexico City (Fig. 1).

Data were recorded in an Excel spreadsheet, and SPSS version 21 was used for statistical analysis. Descriptive analyses were performed for demographic variables; qualitative variables were reported as percentages, and quantitative variables were reported as measures of central tendency.

Results

Seventy-four patients with DMD were diagnosed and followed by the Pediatric Neurology service, averaging six patients per year; all were male. Carrier testing was performed in 63.5% (n = 47/74) of mothers, with carrier status confirmed in 57.5% (n = 27/47). In addition, 28.4% (n = 21/74) had a history of one to four affected relatives.

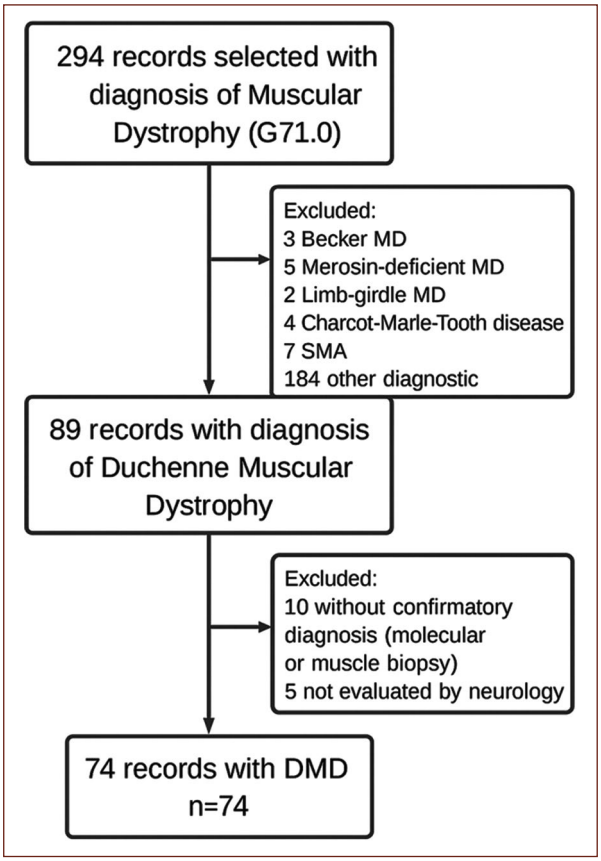

Figure 1. Flowchart of sample selection. Patients with a confirmed diagnosis of Duchenne muscular dystrophy treated at the National Institute of Pediatrics between 2010 and 2020 were included. The selection process involved a review of medical records, applying exclusion criteria such as incomplete diagnosis, loss to follow-up, or lack of clinical or genetic confirmation, resulting in a final number of cases that met the criteria for analysis.

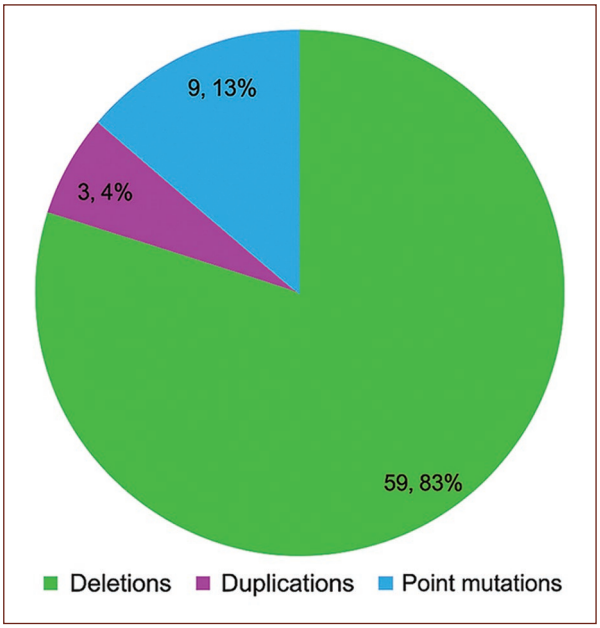

Figure 2. Mutations identified. Most frequent types of mutations detected in the Duchenne muscular dystrophy gene by molecular biology studies.

The age at symptom onset ranged from 2 to 9 years, with a median of 3 years. The first neurology visit and DMD diagnosis occurred at a median age of 7 years. Loss of ambulation was observed between 7 and 14 years, with a median of 10 years.

At the first evaluation, 86% of patients (n = 64/74) were ambulatory. The main clinical manifestations are shown in figure 2; calf hypertrophy was present in 94% (n = 70/74) and Gowers' sign in 87% (n = 65/74).

Serum CK was measured in 82% of patients (n = 61/74), and all had elevated levels ranging from 5.5- to 292-fold the upper limit of normal (20-200 IU/L), with absolute values between 1,102 and 58,497 IU/L. Liver transaminases were measured in 35% (n = 26/74) of patients, all showing elevations > 100 IU/L (normal alanine aminotransferase and aspartate aminotransferase 30-65 IU/L); one case underwent liver biopsy due to suspected liver disease, with a normal result.

A muscle biopsy was performed in 16 patients, all demonstrating the absence of dystrophin on immuno histochemistry.

Regarding the timing of genetic testing, multiplex polymerase chain reaction (PCR), multiplex ligation-dependent probe amplification (MLPA), or gene sequencing was performed. Of these, 3/74 were negative and 71/74 were positive; among the latter, deletions were the most common mutation in 83% (n = 59/71), and 74% of those patients (n = 43/59) had deletions located between exons 45-55, corresponding to the so-called mutational hotspots (Fig. 1). In addition, a second mutational cluster was identified in exons 8-14, present in 13 patients (16.0%). A low-frequency mutational involvement was also observed in the distal region 56-67 (3 patients; 3.7%). The complete exon-by-exon distribution (1-79) is summarized in figure 4.

Oral steroid treatment was administered to 60/74 patients; deflazacort was most frequently used (73%, n = 54), compared to prednisone (8%, n = 6). The mean age at steroid initiation was 6.7 years (standard deviation [SD] 1.98), age at withdrawal was 10.8 years (SD 2.6), and mean duration of treatment was 3.3 years. Only 5 patients were candidates for gene therapy protocols; of these, 3 were treated with ataluren and 2 with viltolarsen.

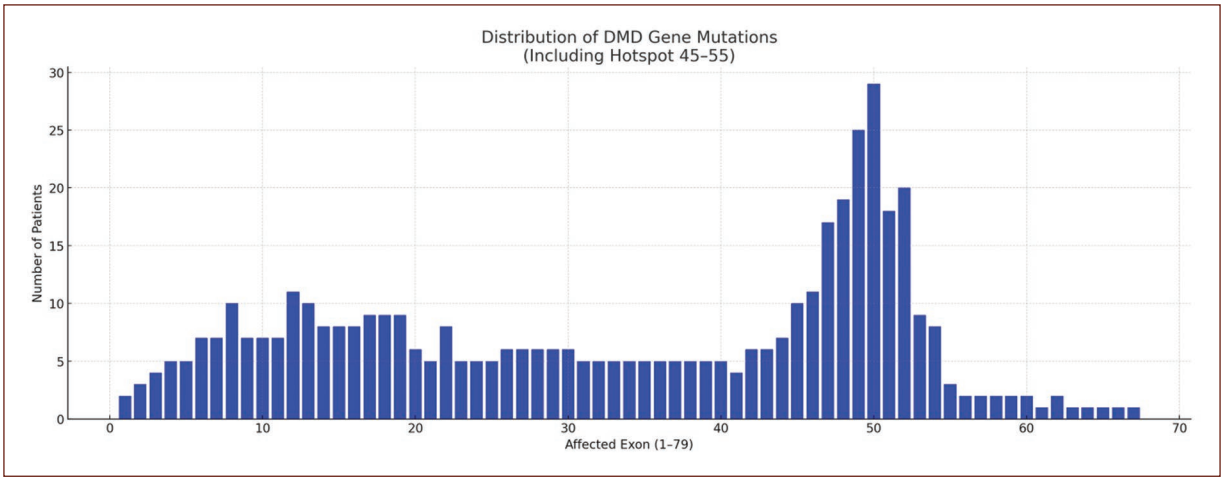

Figure 3. Frequency of pathogenic variants across Duchenne muscular dystrophy (DMD) exons. Distribution of DMD gene mutations across exons 1-79 in the Mexican cohort. The highest mutation density is observed within the distal hotspot (exons 45-55), followed by a secondary cluster in exons 8-14 and a low-frequency distal tail in exons 56-67.

The mean age at onset of comorbidities was as follows: Cardiovascular at 13 years, respiratory at 11 years, orthopedic at 8 years, and endocrine at 10 years. Neuropsychiatric comorbidities most frequently included anxiety and depression, primarily appearing with loss of ambulation and requiring pharmacological treatment and psychiatric follow-up (Table 2).

With respect to loss of ambulation, 9 patients had already lost ambulation before the first visit, and 44 lost ambulation during follow-up between 7 and 14 years of age, with a mean of 10.2 years (SD 1.93). Follow-up was lost in 27 patients, and one death was reported at 16 years of age due to respiratory failure.

Table 1. Frequency of symptoms at the initial evaluation

Symptoms at initial evaluation	Frequency (%)
Abnormal gait	74 (100)
Difficulty climbing stairs	74 (100)
Frequent falls	73 (98.6)
Muscle weakness	73 (98.6)
Calf hypertrophy	70 (94.5)
Gowers' sign	65 (87.8)
Independent ambulation	65 (87.8)
Toe walking	35 (47.2)
Intellectual disability	31 (41.8)

The most common clinical manifestations observed during the initial medical evaluation of patients with Duchenne muscular dystrophy are described.

Discussion

DMD results from mutations in the gene encoding dystrophin; more than 7,000 mutations have been described, making this gene highly susceptible to spontaneous mutations, which have been reported in approximately one-third of cases.[2] In this study, 68.9% (n = 51/74) of the patients had no affected relatives, and carrier status was excluded in 42.5% (n = 20/47) of the mothers tested, suggesting *de novo* mutations, similar to findings reported by Nascimento et al.,[14].

Nascimento et al.[14] noted the absence of symptoms at birth, although DMD may initially present with developmental delay. In our cohort, 66% (n = 49/74) of patients had motor delay and 35% (n = 26/74) had speech delay. The literature also describes that the first symptoms of DMD typically appear between 3 and 5 years of age,[14] which is consistent with the median age at symptom onset found in our study.

According to Alcántara-Ortigoza et al., the initial signs of dystrophinopathies include proximal weakness, hyperCKemia, myopathic findings on electromyography, and dystrophic changes on muscle biopsy; approximately 41.6% of patients met three or more of these criteria.[4] In our study, the primary motor symptoms were frequent falls and difficulty climbing stairs, with CK elevation present in 63% of patients, in agreement with data reported in the literature.

Table 2. Comorbidities in Duchenne muscular dystrophy

System	Condition	Frequency	%
Neuropsychiatric	Intellectual disability	31	41.9
	None	30	40.5
	Epilepsy	2	2.7
	Learning disorder	2	2.7
	Autism	2	2.7
	Depression	2	2.7
	ADHD	2	2.7
	Migraine	1	1.4
	Anxiety disorder	1	1.4
	Anxiety + Depression	1	1.4
Cardiovascular	None	61	82.4
	Unknown	8	10.8
	Heart failure	3	4.0
	Dilated cardiomyopathy	2	2.7
Respiratory	None	41	55.4
	Obstructive sleep apnea/hypopnea	22	29.7
	Recurrent pneumonia	4	5.4
	Unknown	4	5.4
	Obstructive pneumopathy	1	1.4
	Bronchial hyperreactivity	1	1.4
	Adenoid hypertrophy	1	1.4
Gastrointestinal/ nutritional	None	41	55.4
	Obesity	16	21.6
	Unknown	15	20.2
	Malnutrition	9	12.2
	Constipation	6	8.1
	Mastication/ swallowing difficulties	5	6.8
	Gastroesophageal reflux	2	2.7
	Esophageal motility disorder + esophagitis	1	1.4
	Hepatic steatosis	1	1.4
Endocrine	Unknown	51	68.9
	Vitamin D deficiency	11	14.9
	None	8	10.8
	Insulin resistance	4	5.4
	Cushing's syndrome	3	4.1
	Short stature	2	2.7
	Hypothyroidism	1	1.4
	Osteoporosis	1	1.4
Orthopedic	None	33	44.5
	Scoliosis	18	24.3
	Flat feet	13	17.6
	Fractures	7	9.5
	Unknown	2	2.7
	Ankle sprain	1	1.4
	Achilles tendon contracture	1	1.4
	Genu valgum	1	1.4

(Continues)

Table 2. Comorbidities in Duchenne muscular dystrophy *(continued)*

The main clinical conditions associated with Duchenne muscular dystrophy documented during patient follow-up.

Approximately 30% of DMD patients may present with intellectual disability and learning or behavioral problems as noted by Cotton et al.[15] and Thangarajh et al.; however, in this study, 41% (n = 31/74) of patients had intellectual disability as the most common neuropsychiatric comorbidity, which is higher than previously described.[15,16]

The clinical findings in our patients – including gait disturbances, difficulty climbing stairs, muscle weakness, calf hypertrophy, and Gowers' sign – were highly similar to those reported internationally.[9]

The literature indicates that the average age at DMD diagnosis is between 3 and 5 years.[4,5] In our study, care and diagnosis were delayed by approximately 4 years. 63.5% (n = 47/74) of patients were first evaluated at a specialized center during the late ambulatory stage, and only 1% were seen during the presymptomatic stage despite 28.4% (n = 21/74) having at least one affected relative. The mean age at loss of ambulation was 10.2 years, earlier than the 12-14 years reported by Nascimento et al.[14] Interestingly, 17.6% (n = 13/74) of patients were initially diagnosed with flat feet and treated with orthopedic insoles; after lack of improvement, they were referred to neurology and eventually diagnosed

with DMD, which delayed definitive diagnosis as reported by Cammarata-Scalisi et al.,[17].

As part of the diagnostic process, Birnkrant et al. recommend testing serum CK at the slightest suspicion of neuromuscular disease, with levels typically elevated 10- to 100-fold in DMD patients; in this study, CK was elevated 5.5- to 292-fold, exceedingly twice the upper limit described in the literature. Elevated transaminases are common in DMD and have sometimes been investigated as hepatopathy, further delaying final diagnosis. In our cohort, transaminase levels were measured in 35% of patients and were all greater than 100 IU/L; one case required liver biopsy, which was normal.

Molecular diagnosis of DMD is achieved by multiplex PCR, which detects deletions, or MLPA, which also identifies duplications, with the latter considered the most appropriate test according to Elangkovan et al.; if these tests are negative and clinical suspicion remains, gene sequencing is indicated to detect other point mutations.[18] In this study, molecular testing was performed in 87.3% (n = 62/71) using PCR and MLPA; deletions were present in 83% (n = 59), higher than the 70% reported by Birnkrant et al.; 74% (n = 44) of these deletions were located in exons 45-55, corresponding to the gene's so-called hot spots, which is higher than the 47% reported by Duan et al.,[1].

Alcántara-Ortigoza et al. report that a genetic diagnosis was achieved in 80.5% of cases, with dystrophinopathy-associated genotypes predominating in 68% of patients. They also noted a 4.2% rate of false negatives for DMD gene deletions detected by PCR.[4] Escobar-Cedillo et al. analyzed 169 patients using next-generation sequencing and MLPA and found pathogenic variants in 68% of cases; dystrophinopathies were the most common (52.36%), followed by dysferlinopathies (18.40%) and sarcoglycanopathies (14.15%).[5]

Muscle biopsy is reserved for confirming the absence of dystrophin when molecular tests are negative and clinical suspicion remains high;[8] in our study, it was performed in 21.6% (n = 16/74) of patients and confirmed DMD in 3 cases.

The most recent guidelines strongly recommend initiating glucocorticoids when motor skills begin to decline around 4-5 years of age to slow disease progression and prolong ambulation; therapy should continue throughout life as it delays pulmonary and cardiac involvement, reduces scoliosis, and preserves upper-limb strength.[9] In this study, 81% (n = 60/74) of patients were treated with steroids for an average of 3.3 years; mean age at initiation was 6.7 years and mean age at withdrawal was 10.8 years. Of these patients, 73% (n = 54) received deflazacort and 8% (n = 6) prednisone, indicating delayed initiation and early withdrawal despite evidence supporting indefinite use.

Duan et al.[1] report that gene therapy is one of the most promising research directions for DMD; although techniques have advanced considerably and early clinical trial results are encouraging, its utility depends on the specific mutation present. In this study, only 5 patients (6.7%) were candidates for gene therapy: 3 were treated with ataluren and 2 with viltolarsen.

San Martín et al. report a 50.7% probability of survival before age 20.[19] In our study, only one death was documented, although 36% (n = 27/74) of patients were lost to follow-up, indicating a low observed mortality rate but a high rate of attrition.

Despite significant therapeutic advances over the past three decades, there is still no cure for DMD. However, a multidisciplinary approach that addresses medical, surgical, and rehabilitative aspects focused on DMD-associated morbidity can improve the natural history of the disease, leading to better quality of life and increased survival.[20]

Based on the findings in our Mexican cohort, the mutational distribution of the *DMD* gene shows a clear predominance in the 45-55 exon region, which is consistent with what has been reported in the international literature.[1-3,21] We also identified a second mutational peak in exons 8-14, present in 13 of 81 patients (16.0%), which aligns with the proximal hotspot previously described in Latin American and multicenter studies.[21,22] In a Colombian series, approximately 20% of deletions were located outside the classical hotspot regions,[4] whereas European and Asian cohorts have reported mutations in exons > 55 or < 8, although with lower frequencies (~2-5%).[22,23]

Consistently, in our cohort, we also detected mutations in exons 56-67 in 3 patients (3.7%), confirming that distal alterations > 55 are relatively uncommon, yet clinically relevant for a comprehensive understanding of the mutational spectrum.[22,23]

The position of the mutation has a direct impact on therapeutic eligibility, since exon-skipping therapies targeting exons 45, 51, or 53, as well as read-through therapy (ataluren) and future micro-dystrophin approaches, depend on the specific mutation type and location.[18,24,25] Therefore, the presence of a non-negligible proportion of pathogenic variants outside the currently approved exon targets underscores the need to expand access to comprehensive molecular testing (including full *DMD* gene sequencing) and to develop individualized therapeutic strategies tailored to national and regional needs.[4,6,24,25]

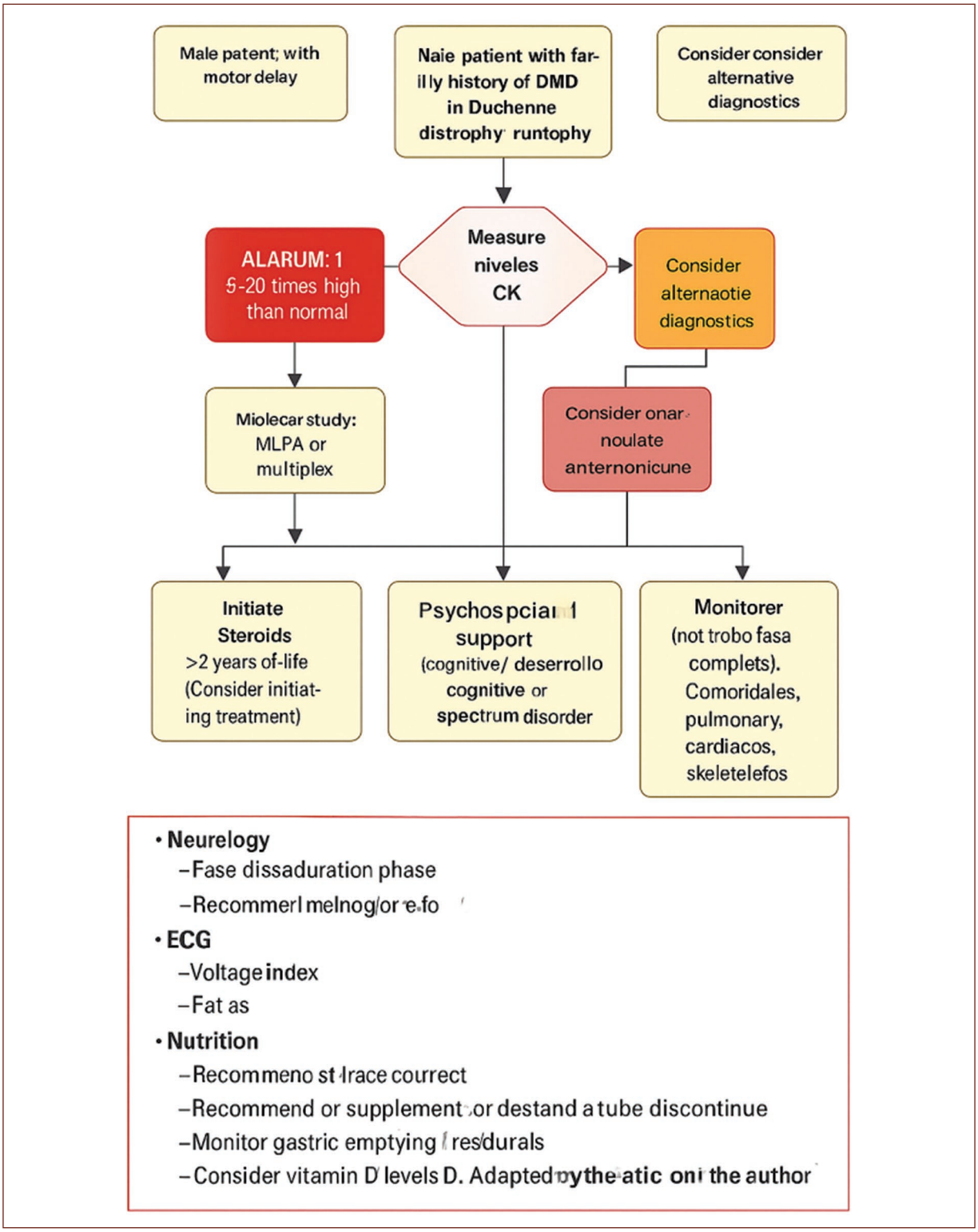

Figure 4. Diagnostic and follow-up flowchart in Duchenne muscular dystrophy. Adapted by the author. The proposed clinical algorithm for patients with suspected Duchenne muscular dystrophy (DMD) begins with detecting clinical signs such as motor delay or abnormal liver enzymes, followed by CK testing and genetic studies (Multiplex Ligation-Dependent Probe Amplification and DMD gene sequencing). If necessary, a muscle biopsy is performed. Treatment includes corticosteroids, angiotensin-converting enzyme inhibitors, supplements (calcium and vitamin D), rehabilitation, and psychosocial support. Multidisciplinary follow-up is established annually with specialties including pulmonology, cardiology, endocrinology, and orthopedics, with functional assessments adapted according to the stage of the disease.[10]

Conclusions

Despite advances in diagnostic and therapeutic strategies, patients with DMD in our setting continue to experience unfavorable outcomes, most likely due to low clinical suspicion, which leads to delayed diagnosis and late initiation of treatment at more advanced stages of the disease.

Primary care physicians must maintain a high index of suspicion for neuromuscular pathology in the presence of motor developmental delays and obtain CK measurements to reduce the considerable gap between symptom onset, diagnosis, and management.

To improve quality of life and outcomes for patients with DMD, institutional protocols are needed to support early detection and establish standardized diagnostic and therapeutic criteria, as well as multidisciplinary care guided by up-to-date scientific evidence to prevent and manage complications.

Long-term corticosteroid therapy remains the cornerstone of management, even in non-ambulatory stages, complemented by multidisciplinary symptomatic interventions that can favorably modify the natural course of the disease.

To facilitate early identification, diagnostic and management of DMD, a diagnostic and follow-up flowchart is proposed (Fig. 3), adapted by the author as a practical guide to assist clinicians in streamlining early recognition and delivering comprehensive care.

Funding

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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ORIGINAL ARTICLE

Development and pilot validation of a Dyspraxia Evaluation Battery

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Abstract

Objective: *The objective of this study was to describe the psychometric properties of the pilot phase of the Battery for the Assessment of Dyspraxia in a sample of 200 Mexican children, composed exclusively of neurotypical participants between 2 and 6 years of age.* **Methods:** *The test was developed based on the theoretical principles of dyspraxia proposed by Castillo-Sánchez Lara. Participants were selected through convenience sampling from public and private schools in three Mexican states. Five scales were constructed according to age groups (2, 3, 4, 5, and 6 years). Each version assessed eight key areas: somatosensory (processing of internal and external stimuli), proprioception (body position in space), body schema (global body awareness), postural control (body control in motion and at rest), orolingual-facial praxis (voluntary movements of facial and orolingual muscles), constructive praxis (visuomotor and spatial coordination), somatopraxis (precise execution of voluntary movements), and visual assessment (active visual search).* **Results:** *Statistical analyses were performed using Cronbach's alpha coefficient. The results showed acceptable reliability levels in most scales ($\alpha > 0.7$).* **Conclusions:** *The battery for the assessment of dyspraxia demonstrated adequate psychometric properties in a preschool sample and in detecting alterations in underlying components. The findings support its application in the development and implementation of neuropsychological rehabilitation programs.*

Keywords: *Dyspraxia. Childhood. Apraxia. Assessment.*

Desarrollo y validación piloto de una Batería para la Evaluación de la Dispraxia

Resumen

Objetivo: *Describir las propiedades psicométricas de la fase de piloteo de la Batería para la Evaluación de las Dispraxias, en una muestra de 200 niños mexicanos, compuesta exclusivamente por participantes neurotípicos entre 2 y 6 años.* **Métodos:** *La prueba se fundamentó con los principios teóricos de la dispraxia propuestos por Castillo-Sánchez Lara. Los participantes fueron seleccionados mediante muestreo por conveniencia procedentes de escuelas públicas y privadas en tres estados de México. Se construyeron cinco escalas según grupos de edad (2, 3, 4, 5 y 6 años). Cada edición evaluó ocho áreas clave: somatosensorial (procesamiento de estímulos internos y externos), propiocepción (ubicación del cuerpo en el espacio), esquema corporal (conciencia global del cuerpo), control postural (control del cuerpo en movimiento y reposo),*

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praxia orolinguofacial (movimientos voluntarios de músculos faciales y orolinguales), praxia constructiva (coordinación visomotora y espacial), somatopraxia (ejecución precisa de movimientos voluntarios) y exploración visual (búsqueda visual activa). **Resultados:** *Los análisis estadísticos se realizaron mediante el coeficiente alfa de Cronbach. Los resultados mostraron niveles de confiabilidad aceptables en la mayoría de las escalas ($\alpha > 0.7$).* **Conclusiones:** *La batería para la Evaluación de las Dispraxias demostró adecuadas propiedades psicométricas en una muestra de preescolares y en la detección de alteraciones en los componentes subyacentes. Los resultados respaldan el desarrollo e implementación de programas en rehabilitación neuropsicológica.*

Palabras clave: *Dispraxia. Infancia. Apraxia. Evaluación.*

Introduction

Dyspraxia is a disorder characterized by difficulties in performing voluntary actions in the absence of evident neurological damage.[1] Children with dyspraxia exhibit deficits in the organization of intentional movements,[2] which affect the development of cognitive processes,[3] as praxis is involved in their acquisition, organization, and execution,[4,5] Despite its relevance, specialized instruments for assessing praxis are limited and mostly oriented toward adult populations.[6]

In 1975, Gubbay developed a test to assess praxis skills in children with motor clumsiness of unclear neurological origin. However, its use was criticized for lacking specificity in differentiating dysfunctions in other areas such as the cerebellum or basal ganglia.[7,8] Similarly, Ayres, through the sensory integration and praxis test (SIPT), emphasized the importance of sensory perception, praxis, bilateral integration, and balance, incorporating non-standardized clinical observations such as sensory reactivity and postural mechanisms.[9,10] This approach fostered a more holistic and functional understanding of child development. However, the SIPT only assesses children over 4 years of age, leaving a diagnostic gap in earlier developmental stages.

The underdiagnosis of dyspraxia can be attributed to structural, professional, and cultural factors, such as the lack of validated instruments, diagnostic overlap with other developmental disorders, and limited professional training in early praxis assessment.[3,11] This situation perpetuates the invisibility of the disorder and delays timely intervention. The battery for the assessment of dyspraxia is based on the PAINT Model,[12] inspired by the theoretical principles of Luria and supported by neuroanatomical foundations. Praxis is understood as the result of a complex interaction among different cortical and subcortical structures, as well as the multisensory integration required for the organization and execution of voluntary movement. This battery proposes a comprehensive assessment of the somatosensory, proprioceptive, visual, body schema, and postural control systems – domains essential for praxis functioning.[4] This study aimed to describe the psychometric properties of the pilot phase of the Battery for the Assessment of Dyspraxia in a sample of 200 Mexican children, composed exclusively of neurotypical participants between 2 and 6 years of age.

Materials and methods

The study employed an instrumental, cross-sectional, and non-experimental design with a quantitative approach. Its objective was to describe the psychometric properties of the pilot phase of the battery.

Subjects

The sample comprised 200 neurotypical children (99 boys and 101 girls) aged between 2 and 6 years old at the time of test administration (June 2023 to December 2024). The mean age was 4.04 years (Standard deviation = 1.39). The age distribution was as follows: 38 participants aged 2 years (19%), 38 aged 3 years (19%), 39 aged 4 years (19.5%), 48 aged 5 years (24%), and 37 aged 6 years (18.5%).

Based on age ranges, five groups were formed:

- Group 1 (2 years olds): 38 participants, 20 boys (52.6%) and 18 girls (47.4%).
- Group 2 (3 years olds): 38 participants, 18 boys (47.4%) and 20 girls (52.6%).
- Group 3 (4 years olds): 39 participants, 19 boys (48.7%) and 20 girls (51.3%).
- Group 4 (5 years olds): 48 participants, 22 boys (45.8%) and 26 girls (54.2%).
- Group 5 (6 years olds): 37 participants, 20 boys (54.1%) and 17 girls (45.9%).

A convenience sampling method was used, based on participant availability and accessibility, as well as to optimize human and material resources and reduce data collection time within the limited study period. Participants were recruited from public and private schools located in Mexico City, the State of Mexico,

and Veracruz, according to institutional accessibility and authorization. However, this characteristic represents an important limitation regarding the external validity of the study. Given the relatively small sample size, the results cannot be generalized to the entire Mexican child population. The use of a reduced sample was due to limited access to children with dyspraxia and to the exploratory nature of this initial validation (pilot phase), which main objective at this stage was to analyze the sensitivity, relevance, coherence, and comprehension of the items rather than to achieve full standardization.

This approach allowed the inclusion of children who met the previously established eligibility criteria and who were available at the time of data collection. Inclusion criteria required that children be between 2 years, 0 months and 6 years, 11 months of age. Participants had to be enrolled in early education programs in Mexico and had no learning, behavioral, or neurodevelopmental disorders, according to information provided by the schools. Socioeconomic level was not considered as an inclusion or exclusion criterion.

Procedure

The validation process of the instrument was conducted in multiple phases. Initially, a preliminary version was developed based on a theoretical review of the construct and developmental criteria aligned with the PAINT Model. Experts in dyspraxia then evaluated each item for clarity, relevance, and pertinence, refining the instrument for conceptual and linguistic adequacy in pediatric population.

The final version was administered to preschool children from educational institutions in Veracruz, the State of Mexico, and Mexico City between June 2023 and December 2024. Data collection took place in person, with approval from educational authorities and the Ethics Committee of Reaprende Neuropsychological Rehabilitation Center, and informed consent from parents or guardians. Assessments were conducted individually under standardized, distraction-free conditions to ensure comprehension and minimize external influences.

The administration was carried out by professionals in neuropsychology from Reaprende Neuropsychological Rehabilitation Center. All examiners received prior training in the standardized administration of the dyspraxia evaluation battery, and continuous supervision throughout the process ensured procedural consistency and objectivity.

Measurement instrument

Dyspraxia assessment battery was constructed according to the praxis principles of the PAINT Model,[4] which is based on the theoretical framework of A.R. Luria. This battery aims to identify the presence of dyspraxia and alterations in the underlying components. It consists of eight measurement scales: somatosensory, proprioception, body schema, postural control, orofacial praxis, constructive praxis, somatopraxis, and visual, composed approximately of 40 items that vary according to age. The items included in the assessment were developed by the author based on activities of daily living. The test is administered according to the child's age and includes five versions corresponding to ages 2, 3, 4, 5, and 6 years old.

Considering that praxis functions develop progressively during the early years of life,[5] five versions of the test were designed and adjusted for each age group. This decision reflects the developmental nature of praxis skills, which are acquired and refined as children's motor, perceptual, and cognitive systems mature. The period between 2 and 6 years of age represents a critical window for the acquisition and consolidation of praxis, sensory, and perceptual abilities.[12] During this stage, children exhibit rapid maturation of the central nervous system, particularly in areas related to sensory integration, visuomotor coordination, and movement planning.[13,14] Adapting the test items and task demands to each age range allows for a more accurate assessment of the expected developmental level, avoiding both overestimation and underestimation of children's performance.

It is essential to assess dimensions such as somatosensory processing, proprioception, and body schema, as these components enable children to recognize their own bodies and orient their movements in space.[15-17] Postural control, as well as orofacial, constructive, and somatopraxic praxis, have been shown to be key indicators of a child's ability to execute sequential actions with intention and precision.[15,18] The inclusion of the Visual scale allows for the evaluation of visual search and attention abilities, which are closely related to perceptual organization and movement planning.[19]

Together, these scales provide a comprehensive and ecologically valid assessment of praxic development in children, allowing for the early detection of potential disruptions that may impact learning and autonomy. Table 1 illustrates representative items from the eight evaluation scales comprising the battery for the assessment of dyspraxia, along with the corresponding administration procedures across the four modalities described below.

Table 1. Distribution of items according to the scales of the dyspraxia assessment battery

Scale	Description	Examples of items	Application method and items
Somatosensory	Assesses the processing of internal and external stimuli	2 years old Tolerates hair grooming without complaining 3 years old Tolerates getting hands dirty 4 years old Tolerates tight-fitting clothing 5 years old Accurately identifies the finger that was touched 6 years old Accurately identifies whether a circle or a cross is traced on the back	PR (Items 1-6) PR (Items 1-4) PR (Items 1-6) PR (Items 1 and 2) and OP (Items 4-6) PR (Item 1), I (Item 6) and OP (Items 2, 3, 4, 5, 7-9)
Proprioception	Evaluates body position in space	2 years old Demonstrates postural adjustment in response to discomfort 3 years old In a seated position, raises and lowers both knees 4 years old Hand resistance to external displacement 5 years old Demonstrates upward and downward movement of the foot while standing 6 years old Walks backward, measuring the distance between the hoops	PR (Item 7) and I (Items 8-11) PR (Item 5), VC (Items 6-16) and OP (Item 17) PR (Items 7 and 8) and I (Items 9-15) I (Items 7-9) VC (Items 10 and 11)
Body schema	Assesses the mental representation of the body	2 years old Rolls over (still bends the knees) 3 years old Performs lateral hip movements 4 years old Raises and lowers the shoulders 5 years old Lying prone, moves arms and legs upward 6 years old Moves the shoulders backward	VC (Items 12-14) I (Items 18 and 23) and VC (Items 19-22) I (Items 16 and 17) and VC (Item 18) I (Items 10, 13 and 16) and VC (Items 11, 12, 14 and 15) VC (Items 12-16)
Postural control	Evaluates body management during movement and rest	2 years old Rises quickly from the floor 3 years old While lying on the floor, abducts and adducts the legs 4 years old Jumps from one hoop to another without falling 5 years old Performs crossover steps forward and backward 6 years old Performs rhythmic hip movements using a hoop	VC (Items 15-19) VC (Items 24-29) VC (Items 19-22) VC (Items 17, 18 and 21-14) and I (Items 19 and 20) VC (Items 17-21)
Orolingual-facial praxis	Assesses voluntary movements of facial and orolingual muscles	2 years old Blows out a birthday candle 3 years old Uses the tongue to clean the lips 4 years old Make a loud kissing sound 5 years old Bite your lower lip with your upper teeth 6 years old Open your mouth, stick out your tongue, and curl it upward	I (Items 20-23) and OP (Items 24 and 25) I (Items 30-33) VC (Items 23-28) VC (Items 22-27) VC (Items 22-27)

(Continues)

Table 1. Distribution of items according to the scales of the dyspraxia assessment battery *(continuation)*

Scale	Description	Examples of items	Application method and items
Constructive praxis	Assesses the ability to integrate visuospatial processes with pragmatically oriented actions	2 years old Joins two cookies to make a cookie sandwich 3 years old Reproduces a vertical line 4 years old Cuts out squares and circles 5 years old Reproduces geometric patterns 6 years old Makes a paper hat	I (Item 26) I (Items 34-36) OP (Item 29) and I (Item 30) OP (Item 28) and I (Item 29) VC (Item 28) and OP (Items 29-31)
Somatopraxis	Evaluates the accurate performance of voluntary movements	2 years old Can unwrap a candy 3 years old Moves through a tunnel using crawling 4 years old Can roll over while lying on the floor 5 years old Sharpens a pencil 6 years old Folds a t-shirt	VC (Item 27) and OP (Items 28-38) OP (Items 37-47) OP (Items 32, 34, 35, 37 a 39), VC (Items 31 y 33) and PR (Item 36) OP (Items 30-33), I (Item 34) and RP (Item 35) OP (Items 32-34 and 37) and RP (Items 35 and 36)
Visual scale	Visual perception processes are assessed (alertness, visual scanning, visual tracking, and visual exploration)	2 years old Tracks a moving rattle 3 years old Tracks a balloon and strikes it with one hand 4 years old Performs throwing and catching of a medium ball 5 years old Tracks multiple bubbles visually 6 years old Discriminates figure-ground	OP (Items 39-44) OP (Items 48-52) OP (Items 40-42 and 44) and VC (Item 43) OP (Items 36-41) VC (Items 38, 44-47) and OP (Items 39-43)

OP: present object; VC: verbal command; PR: parent/caregiver report.

Scoring criteria

The administration time for each version of the battery ranges from 45 to 60 min, depending on the child's age. Structured according to age group and corresponding scale, the items can be administered in four modalities: present object, assessing interaction with and use of objects; verbal command, evaluating the ability to follow instructions; Imitation (I), involving reproduction of actions through songs and play; and parent/caregiver report, addressing daily activities such as feeding, hygiene, and dressing.

Responses are scored on a three-point scale: 0 = incorrect (did not perform), 1 = partial attempt (tried but did not complete), and 2 = correct (performed successfully).

Examiner requirements

The administration of the dyspraxia test in early childhood requires professionals trained in child neuropsychology or related fields, with expertise in neuropsychological maturation, motor development, and praxis, as well as experience in assessing and observing preschool-aged children. Clinical experience further enhances the accuracy of interpretation.

Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences Statistics (version 26). Construct validity was assessed through Fleiss' Kappa, which guided judges' decisions on item inclusion. Internal consistency was examined using descriptive statistics and independent-samples t-tests ($p < 0.05$) to identify gender differences in total scores. Cronbach's alpha was calculated to evaluate the reliability of each subscale across the five battery versions. In addition, age-specific normative tables were developed to facilitate interpretation of results for each version.

Results

Internal consistency

To assess internal consistency reliability, Cronbach's alpha coefficient was calculated for each of the five versions of the instrument, corresponding to different age groups, allowing for the evaluation of the psychometric stability of the tool across developmental stages.

For most age groups, Cronbach's alpha coefficients exceeded the commonly accepted threshold of 0.70, indicating satisfactory internal consistency. Specifically, the values obtained were as follows:

- 2 years old: $\alpha = 0.843$
- 3 years old: $\alpha = 0.600$
- 4 years old: $\alpha = 0.874$
- 5 years old: $\alpha = 0.779$
- 6 years old: $\alpha = 0.828$

Although the 3-year-old group exhibited a coefficient slightly below the 70 threshold (0.60), this value is still considered acceptable, particularly given the developmental variability, attentional factors, and early stage of psychomotor organization at that age.[20] These results provide strong empirical support for the internal coherence of the scale, especially in the 2-, 4-, 5-, and 6-year-old groups, where reliability coefficients were notably robust.

It is important to mention that, due to the pilot nature of this study and the limited sample size, it was not possible to perform exploratory or confirmatory factor analyses, test-retest reliability, or concurrent validity; these stages will be addressed in future studies with larger samples.

Construct validity

The expert panel consisted of 10 academics holding graduate degrees in neuropsychology from various Mexican universities. To evaluate the five versions of the questionnaire developed, a Likert-type format was employed, supplemented with open-ended questions to gather more detailed feedback (Supplementary data).

Inter-rater reliability (Fleiss' Kappa)

Inter-rater agreement was assessed using Fleiss' Kappa, which evaluates the degree of concordance among a fixed number of raters assigning categorical ratings to items. This index guided decisions on which items might require modification based on the level of agreement. The following interpretation ranges were applied:[21]

- 0-0.49: Low
- 0.50-0.59: Regular
- 0.60-0.85: Good
- 0.86-1: Excellent

The indices ranged from 0.85 to 1.00, indicating good to excellent reliability. Specifically, the somatosensory (0.86), postural control (0.86), orolingual praxis (0.89), proprioception (0.92), and visual scale (0.94) subscales showed excellent agreement, while the body scheme subscale (0.85) achieved a good level of consistency.

The constructive praxis and somatopraxis subscales both reached perfect agreement (1.00), confirming strong inter-rater consistency and supporting the reliability of the instrument's scoring system. The highest level of agreement was excellent for seven subscales, whereas body scheme showed a good level of agreement.

Gender differences

The proportion of male and female participants within each age group was examined to determine whether statistically significant differences were present. This analysis aimed to verify the gender distribution balance across groups and to rule out potential sampling bias that could affect the interpretation of the normative results.

Comparative analyses were conducted using independent samples t-tests. The results showed no statistically significant differences between boys and girls in any of the age groups analyzed.

p values obtained were as follows:

- 2 years ($p = 0.363$; confidence interval [CI] = –1.40-3.72)
- 3 years ($p = 0.814$; CI = –1.51-1.91)
- 4 years ($p = 0.487$; CI = –3.04-1.48)
- 5 years ($p = 0.434$; CI = –1.46-3.34)
- 6 years ($p = 0.243$; CI = –3.24-0.85)

Norm tables

Normative tables were developed for each version of the scale according to age group, enabling the transformation of raw scores into multiple standardized formats for interpretation. Specifically, raw scores were converted into percentile ranks (Pc), which indicate the relative position of a child's performance within their age group, as well as into standardized Z scores and T scores, allowing for a more precise comparison across individuals and groups. Given the pilot nature of the study, normative tables were partially completed, as some score intervals did not have enough cases for reliable estimates.

This process ensures that the instrument accounts for age-related developmental differences, providing age-appropriate norms that enhance the interpretability of the results in both clinical and educational contexts. The full set of normative data is presented in tables 2-6, corresponding to each of the five age-specific versions of the instrument.

Performance levels	Percentile range	Clinical meaning
Superior	> 75	Exceptional performance
High average	60-74	High practical efficiency
Average	40-59	Expected functioning
Low average	26-39	Possible mild difficulties
Low	< 25	Clinically significant deficit

Cutoff points are classified into five interpretive levels: superior, high average, average, low average, and low. For example, a 4-year-old child at the 10th percentile demonstrates a clinically significant deficit, indicating that their praxis and coordination performance falls below normative expectations and warrants intervention.

Discussion

The results obtained show acceptable internal consistency indexes across most age groups and a scale structure coherent with the proposed theoretical model. These findings suggest adequate preliminary reliability and support the relevance of the selected components for assessing praxic development in early childhood. In the reliability analysis by age, the version for 3-year olds showed the lowest internal consistency among all scales. Despite this, it is considered acceptable for a pilot instrument with very young children due to high variability in motor behavior, attention, and comprehension.[20] This finding underscores the challenges of assessing younger children and highlights the need to adapt item complexity and clarity, as well as to increase sample size and diversity in future studies, to enhance reliability and construct validity.

This study addresses the notable lack of specialized instruments for assessing dyspraxia in pediatric populations. This scarcity may be attributed to several factors, including the tendency to regard early-childhood dyspraxia as an "invisible" disorder. Its symptoms are often underestimated or misinterpreted as mere "clumsiness" or "lack of coordination" attributed to the child's young age or apparent inability to perform intentional actions. Clinically, the battery offers a promising tool for assessing motor and praxic development, enabling early identification of difficulties in motor planning and execution. It can guide neuropsychological interventions to strengthen sensorimotor processes,

Table 2. Normative scores for the dyspraxia scale for 2-year-olds

Pc	Direct score	Pc	z	T
1	≤ 75	1	–2.63	24
5	76-77	5	–2.15	28
10	78	10	–1.91	31
15	79-81	15	–1.25	38
20	82	20	–0.89	41
25	**83-84**	**25**	**–0.46**	**45**
30	85	30	0.10	51
35	86	35	0.10	51
40	**-**	**40**	**-**	**-**
45	87	45	0.35	54
50	-	50	-	-
55	-	55	-	-
60	**-**	**60**	**-**	**-**
65	-	65	-	-
70	-	70	-	-
75	**-**	**75**	**-**	**-**
80	-	80	-	-
85	-	85	-	-
90	88	90	0.60	56
91	-	91	-	-
92	-	92	-	-
95	-	95	-	-
96	-	96	-	-
97	-	97	-	-
98	-	98	-	-
99	-	99	-	-

Bold values indicate clinical cutoffs; > 40 is interpreted as a normal level. The 25th percentile indicates the cutoff for significant deficit levels in praxis execution. The presence of this cutoff suggests that scores below the 25th percentile represent a significant level of dyspraxia.

Table 3. Normative scores for the dyspraxia scale for 3-year-olds

Pc	Direct score	Pc	z	T
1	≤ 104	1	–2.38	26
5	105	5	–2.38	26
10	106	10	–1.64	34
15	107	15	–1.33	37
20	108	20	–0.97	40
25	**109-110**	**25**	**–0.90**	**41**
30	-	30	-	-
35	111	35	0.21	52
40	**-**	**40**	**-**	**-**
45	-	45	-	-
50	-	50	-	-
55	-	55	-	-
60	**-**	**60**	**-**	**-**
65	-	65	-	-
70	-	70	-	-
75	**-**	**75**	**-**	**-**
80	-	80	-	-
85	-	85	-	-
90	112	90	0.58	56
91	-	91	-	-
92	-	92	-	-
95	-	95	-	-
96	-	96	-	-
97	-	97	-	-
98	-	98	-	-
99	-	99	-	-

Bold values indicate clinical cutoffs; > 40 is interpreted as a normal level. The 25th percentile indicates the cutoff for significant deficit levels in praxis execution. The presence of this cutoff suggests that scores below the 25th percentile represent a significant level of dyspraxia.

Table 4. Normative scores for the dyspraxia scale for 4-year-olds

Pc	Direct score	Pc	z	T
1	≤ 82	1	–3.94	11
5	83-90	5	–2.03	30
10	91-95	10	–0.84	42
15	96-97	15	–0.36	46
20	98-99	20	0.36	54
25	**-**	**25**	**-**	**-**
30	-	30	-	-
35	-	35	-	-
40	**-**	**40**	**-**	**-**
45	-	45	-	-
50	-	50	-	-
55	-	55	-	-
60	**-**	**60**	**-**	**-**
65	-	65	-	-
70	-	70	-	-
75	**-**	**75**	**-**	**-**
80	-	80	-	-
85	-	85	-	-
90	100	90	0.36	54
91	-	91	-	-
92	-	92	-	-
95	-	95	-	-
96	-	96	-	-
97	-	97	-	-
98	-	98	-	-
99	-	99	-	-

Bold values indicate clinical cutoffs; > 40 is interpreted as a normal level. The 25th percentile indicates the cutoff for significant deficit levels in praxis execution. The presence of this cutoff suggests that scores below the 25th percentile represent a significant level of dyspraxia.

tonic regulation, and visuomotor coordination. In educational settings, it serves as a screening and monitoring tool, providing teachers and counselors with information to tailor evidence-based strategies and support early intervention.

Compared with classical instruments based on Liepmann's model, which focus on ideomotor, ideational, constructive apraxias, verbal apraxias,[22] and view deficits as failures in action execution mechanisms,[23,24] the battery for the assessment of dyspraxias offers an innovative, multidimensional approach. It integrates rarely considered aspects in early childhood, such as somatosensory processing, proprioception, body schema, postural control, somatopraxis, and orofacial and constructive praxis, providing a broader understanding of intentional action and linking

Table 5. Normative scores for the dyspraxia scale for 5-year-olds

Pc	Direct score	Pc	z	T
1	≤ 62-69	1	–3.52	15
5	70	5	–1.88	31
10	71-74	10	–1.07	39
15	75	15	–0.74	43
20	76-77	20	–0.44	46
25	**78**	**25**	**–0.19**	**48**
30	-	30	-	-
35	-	35	-	-
40	**79**	**40**	**–0.06**	**49**
45	-	45	-	-
50	80	50	0.23	52
55	81	55	0.43	54
60	**-**	**60**	**-**	**-**
65	-	65	-	-
70	-	70	-	-
75	**-**	**75**	**-**	**-**
80	-	80	-	-
85	-	85	-	-
90	82	90	0.64	56
91	-	91	-	-
92	-	92	-	-
95	-	95	-	-
96	-	96	-	-
97	-	97	-	-
98	-	98	-	-
99	-	99	-	-

Bold values indicate clinical cutoffs; > 40 is interpreted as a normal level. The 25th percentile indicates the cutoff for significant deficit levels in praxis execution. The presence of this cutoff suggests that scores below the 25th percentile represent a significant level of dyspraxia.

Table 6. Normative scores for the dyspraxia scale for 6-year-olds

Pc	Direct score	Pc	Z	T
1	≤ 78	1	–3.89	11
5	79-84	5	–2.19	28
10	85-90	10	–0.55	44
15	91	15	–0.12	49
20	92	20	–0.12	49
25	**93**	**25**	**0.15**	**51**
30	-	30	-	-
35	-	35	-	-
40	**-**	**40**	**-**	**-**
45	-	45	-	-
50	-	50	-	-
55	-	55	-	-
60	**-**	**60**	**-**	**-**
65	-	65	-	-
70	-	70	-	-
75	**-**	**75**	-	-
80	-	80	-	-
85	-	85	-	-
90	94	90	0.42	54
91	-	91	-	-
92	-	92	-	-
95	-	95	-	-
96	-	96	-	-
97	-	97	-	-
98	-	98	-	-
99	-	99	-	-

Bold values indicate clinical cutoffs; > 40 is interpreted as a normal level. The 25th percentile indicates the cutoff for significant deficit levels in praxis execution. The presence of this cutoff suggests that scores below the 25th percentile represent a significant level of dyspraxia.

perception, movement, and motor planning. However, results should be interpreted cautiously, as the study included only neurotypical children and the sample is not fully representative of the Mexican child population, limiting external validity and generalizability.

A further limitation of this study is the absence of clinical comparison groups, which are essential for future validation. Including children with confirmed neurodevelopmental disorders, such as autism spectrum disorder or praxic difficulties, would allow assessment of discriminant validity and sensitivity in detecting motor planning and execution deficits, while informing individualized clinical and educational interventions. Prospectively, the incorporation of a vestibular scale is considered

relevant, based on evidence highlighting the importance of the vestibular system in movement organization, spatial orientation, and tonic regulation necessary for praxic functioning.[9,15] This addition would provide a more comprehensive evaluation of praxic functions. This pilot phase lays the groundwork for a systematic methodology for evaluating dyspraxia and developing targeted interventions according to each child's needs.

Conclusion

This pilot study provides preliminary evidence supporting the reliability and theoretical coherence of the Battery for the Assessment of Dyspraxia in early childhood. The results obtained from a sample of 200 neurotypical children indicate adequate internal consistency in most dimensions of the battery ($\alpha > 0.70$), as well as a factorial structure consistent with the proposed theoretical framework (PAINT Model), supporting the relevance of the selected components for the assessment of praxic development.

The proposed battery represents a relevant contribution, in light of the limited availability of specialized instruments for the assessment of dyspraxia in children, as it adopts a multidimensional approach that integrates aspects commonly underrepresented in traditional models. Its clinical application demonstrates strong potential for the early detection of difficulties in areas such as somatosensory, proprioception, body schema, postural control, orolingual-facial praxis, constructive praxis, somatopraxis, and visual assessment, enabling the development of targeted interventions according to each child's needs. Future studies should expand the sample size and ensure greater representativeness, in order to strengthen external validity and support the generalization of the results.

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

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

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.25000046. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Cost-effectiveness of thrombolysis vs. standard care for stroke in a public hospital in Bogotá

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Abstract

Objective: *Evaluate the cost-effectiveness of intravenous thrombolysis in the treatment of the ischemic stroke compared to standard medical management, in a public hospital in Bogotá, during the period from January to December 2024.* **Methods:** *Observational, cross-sectional study with retrospective data collection, using a sample of patients with ischemic stroke who received intravenous thrombolysis and those who did not, at Kennedy Hospital in Bogotá, Colombia. An economic evaluation was conducted to estimate the incremental cost-effectiveness ratio (ICER) of intravenous thrombolysis compared to standard medical management.* **Results:** *The number of patients who received thrombolysis was 82, while 156 patients received standard medical management. The average cost was $13,316,428.31 (3.269,77 USD) (SD $9,147,043/2.246 USD) for the thrombolysis group and $12,813,094 (3.146,17 USD) (SD $12,261,577/3.010 USD) for the non-thrombolysis group. The thrombolysis group showed a gain of 0.27 quality-adjusted life years (QALYs) with a higher cost of $503,334 (123,59 USD) compared to the standard medical management group, resulting in an ICER of $1,864,201 (457,74 USD) per QALY. The mean utility of 5.9 (SD 4.7) [95% confidence interval [CI]: 1.52–10.27; p = 0.16] for the thrombolyzed group, while for the non-thrombolyzed group, the mean was 5.35 (SD 4.6) [95% CI: 1.03–9.68; p = 0.23], the mean delta utility was 0.54 (SD 0.28) [95% CI: 0.28–0.80; p = 0.02] and the mean ICER per QALY was –1,473,833 (SD 1,656,379) [95% CI: –3,212,096 to 264,430; p = 0.81].* **Conclusions:** *Thrombolytic therapy is associated with greater cost-effectiveness, better clinical outcomes, and reduced disability compared to standard medical management without thrombolytic therapy.*

Keywords: *Stroke. Reperfusion. Thrombolysis. Cost-effectiveness analysis.*

Costo-efectividad de la trombólisis vs. tratamiento estándar para el ACV en un hospital público de Bogotá

Resumen

Objetivo: *Evaluar la costoefectividad de la trombólisis en el tratamiento del ACV isquémico, en comparación con el manejo médico estándar, en un hospital público de Bogotá, durante el período de enero a diciembre de 2024.* **Métodos:** *Estudio observacional, transversal, con recolección retrospectiva de datos, utilizando una muestra de pacientes con ACV isquémico que recibieron trombólisis endovenosa y aquellos que no la recibieron, en el Hospital de Kennedy en Bogotá, Colombia.*

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Resultados: *El número de pacientes que recibieron trombolisis fue de 82, mientras que 156 pacientes recibieron manejo médico estándar. El costo promedio fue de $13,316,428.31 (3.269,77 USD) (SD $9,147,043/2.246 USD) para el grupo con trombólisis y de $12,813,094 (3.146,17 USD) (SD $12,261,577/3.010 USD) para el grupo sin trombólisis. El grupo con trombólisis mostró una ganancia de 0.27 AVAC (QALYs) con un costo adicional de $503,334 (123,59 USD) en comparación con el grupo de manejo médico estándar, resultando en una RCEI de $1,864,201 (457,74 USD) por AVAC. La utilidad media fue de 5.9 (DE 4.7) [IC 95%: 1.52–10.27; p = 0.16] para el grupo trombolizados, mientras que para el grupo no trombolizados fue de 5.35 (DE 4.6) [IC 95%: 1.03–9.68; p = 0.23]; la diferencia media de utilidad (delta) fue de 0.54 (DE 0.28) [IC 95%: 0.28–0.80; p = 0.02] y la RCEI media por AVAC fue de –1,473,833 (DE 1,656,379) [IC 95%: –3,212,096 a 264,430; p = 0.81].*
Conclusiones: *La terapia trombolítica se asocia con una mayor costoefectividad, mejores resultados clínicos y menor discapacidad en comparación con el manejo médico estándar sin trombólisis.*

Palabras clave: *Accidente cerebrovascular. Reperfusión. Trombólisis. Análisis de costo-efectividad.*

Introduction

Stroke is one of the leading causes of mortality worldwide. According to the World Health Organization, more than 5 million people die each year from stroke, making it the second leading cause of death and the primary cause of disability in adults. In Colombia, stroke was reported among the top five causes of mortality, resulting in 32 deaths/100,000 inhabitants in 2019, which represented a total of 15,882 deaths from this condition.[1,2]

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has long been the evidence-based treatment for acute ischemic stroke. However, it must be administered within the first 4.5 h after the onset of ischemic stroke symptoms. It has certain contraindications and may not provide adequate reperfusion, especially in patients with large vessel occlusion, and may increase the risk of intracranial hemorrhage.[1]

Studies have been conducted to assess both direct and indirect costs. Direct costs include those related to healthcare services, such as preventive care, emergency services, hospitalization, rehabilitation, transportation, prescription medications, and home care; as well as social care costs resulting from residual disability after a stroke. Indirect costs include productivity losses due to reduced working capacity (mortality and morbidity costs associated with stroke).[3]

Although early thrombolysis has been shown to reduce costs within a 5-year horizon, there remains a lack of models that consistently incorporate long-term rehabilitation, dependency, and social care.[3]

There remains a significant knowledge gap regarding the cost-effectiveness of thrombolysis in stroke. Most available economic evidence originates from high-income countries, whereas studies from low- and middle-income settings are scarce and show considerable variability in cost estimates.[4] Furthermore, the majority of post-stroke quality of life studies have been conducted in Europe or the United States, frequently converting modified Rankin Scale (mRS) scores to EQ-5D values. In Colombia, local health preference studies are limited; consequently, utility values are often imported from international sources and subsequently adjusted. Many existing evaluations also adopt the health system perspective with short time horizons, frequently omitting indirect costs.[5]

Evaluations based on administrative databases or registries that capture real-world outcomes and costs beyond trial-based assumptions are still limited, particularly outside the United States and Europe.[6]

The clinical benefits of thrombolysis are most evident in the early phase, with significant reductions in mortality and disability during the first weeks to months. Functional outcomes generally stabilize at 90 days, which has become the standard endpoint in pivotal clinical trials such as NINDS, ECASS, and IST-3. Consequently, most randomized trials report 90-day outcomes, providing robust and consistent evidence for the parameterization of economic models.[7]

Extending the time horizon is, however, essential to fully capture the cumulative costs and benefits of thrombolysis. Improvements in disability at 3 months translate into long-term effects on dependency, institutionalization, rehabilitation, and productivity. Without considering extended horizons, estimates risk underrepresenting the potential savings in both healthcare and societal costs. The benefits of avoiding severe dependence, in particular, accrue over time in the form of improved quality of life and reduced expenditures.[8]

In the Colombian context, cost analyses can draw on data from the Health Benefits Plan (PBS/UPC), national fee schedules (SOAT, ISS), and hospital cost reports from both EPS and IPS institutions. These data sources reflect the actual costs of hospitalization, intensive

care, pharmacological treatment (rt-PA), imaging, rehabilitation, and complications, and are therefore essential for contextualizing the economic impact of stroke management with and without thrombolysis.[9]

In the city of Bogotá, there are no available studies evaluating the cost-effectiveness of thrombolysis versus standard medical management in the treatment of stroke patients. Therefore, the objective of this study is to evaluate the cost-effectiveness of intravenous thrombolysis compared to standard medical management in the treatment of the hyperacute and acute phases of ischemic stroke in a hospital in the city of Bogotá during the period from January to December 2024.

Methods

This is an observational, analytical, cross-sectional study framed within the positivist paradigm, using retrospective data collection. An economic evaluation was conducted to estimate the incremental cost-effectiveness ratio (ICER) of intravenous thrombolysis compared to standard medical management.

The study sample included individuals over 18 years of age with ischemic stroke who either received intravenous thrombolysis or standard medical management without thrombolysis, treated at the Kennedy Hospital in Bogotá between January and December 2024.

Sampling design

The entire study population was considered using non-probabilistic sampling from a secondary data source, including medical records, databases, and service invoices of ischemic stroke patients from a referral hospital in Bogotá.

Sample size calculation

A non-probabilistic, convenience sampling method without random assignment was used. Patients included were those listed in the database with a primary diagnosis of ischemic stroke. The original database consisted of 450 patients over a 1-year period. Patients were selected for analysis based on inclusion and exclusion criteria, obtaining a sample of 238 patients.

Inclusion criteria

- Age over 18 years.
- Symptom onset time from 0 to 4.5 h and > 4.5 h.
- Patients diagnosed with ischemic stroke and National Institutes of Health Stroke Scale (NIHSS) scores from 0 to 42.
- Patients who received intravenous thrombolysis.
- Patients who received standard medical management without intravenous thrombolysis.

Exclusion criteria

- Patients with hemorrhagic stroke.
- Patients with stroke mimics.
- Patients lacking sufficient information in the database or medical records.

Data collection technique

The data were obtained from secondary sources, including the hospital's database, medical records, and service invoices from Kennedy Hospital in Bogotá. A formal request letter was submitted to the hospital management, with copies sent to the research and ethics committee for approval, allowing access to the medical records and databases of patients with ischemic stroke. In addition, the project was presented to the cost office to obtain cost data related to hospital admissions and billing. We obtained data on total and differential costs (medications, supplies, hospital stay, specialist consultations, diagnostic tests, and therapies) from the invoices generated during the care of patients with ischemic stroke.

Data analysis

The data extracted into an Excel matrix were exported to SPSS v27 (IBM® SPSS® Statistics 27; IBM Corp., USA) for descriptive statistical analysis. For univariate analysis, qualitative variables were analyzed using absolute and relative frequencies. Quantitative variables were presented using measures of central tendency and dispersion, such as mean and standard deviation. A t-test for means was performed, and the p-value was obtained along with its 95% confidence intervals (CIs).

For the cost-effectiveness analysis, the ICER was calculated, defined as the difference in costs between the intervention and the comparator, divided by the difference in clinical outcomes between the two.

Clinical data were obtained from patient medical records using the institutional software DINAMICA and managed in the Excel matrix. Subsequently, total billing for each ischemic stroke patient between January and

December 2024 was requested from the hospital's cost and marketing department, with prior approval from the institutional cost office. The costs of each intervention intravenous thrombolysis versus standard medical management were analyzed. Each intervention's cost formed the numerator, while the denominator was calculated based on quality-adjusted life years (QALYs) reported in the scientific literature, based on the EQ-5D scale, which assesses five dimensions related to quality of life. Clinical outcomes were assessed using the NIHSS and the mRS for both the intervention and comparator groups.

A cost-effectiveness acceptability curve was generated. A decision tree model was used for the economic evaluation with a time horizon of 3 months, followed by a Markov model extending the time horizon to 20 years. This allowed us to determine which intervention is dominant in terms of cost-effectiveness over the defined period.

The present study was conducted from the health system perspective. Relevant cost components were identified through a micro-costing approach, using invoices generated during each patient's hospital stay (including rt-PA/tenecteplase, computed tomography [CT]/angio-CT, emergency department, intensive care unit, hospital bed-days, consumables, specialist consultations, among others). No adjustment for purchasing power parity was applied, as no cross-country cost comparison was undertaken; instead, all costs in Colombian pesos (COP) were converted into USD using the average official exchange rate (TRM) for 2024.

Utility weights were obtained from the published literature rather than primary data, consistent with the assumptions used in the Markov model. QALYs were estimated based on the EQ-5D instrument and its correspondence with the mRS, by assigning a utility value to each mRS category.

Uncertainty was addressed through the calculation of standard deviations and by conducting a probabilistic sensitivity analysis, represented by a cost-effectiveness acceptability curve that incorporated both utilities and willingness-to-pay thresholds for Colombia. In line with international recommendations, the willingness-to-pay threshold was considered to be between one and three times the gross domestic product per capita. As a reference, we used the threshold estimated by Espinosa et al. (2022), who reported a value of COP 17,000,000 per QALY gained for 2019 in the Colombian health system, given the absence of more recent or 2024-specific estimates.

Results

This study included a total sample of 238 patients, of whom 82 were assigned to the thrombolysis group and 156 to the non-thrombolysis candidate group. Considering the sociodemographic characteristics of the population by group, we found that in the thrombolysis group, 38.5% were male, whereas in the non-thrombolysis group, 69.8% were female. Regarding socioeconomic status, 47.5% of the total population belonged to stratum 2. This distribution pattern remained consistent across both groups. In terms of education level, the majority of the population had completed only primary education, representing 57.6% of the total. With respect to area of residence, both groups were predominantly from urban areas (95.8%) (Table 1). The average age was 66 years for the thrombolysis group and 68 years for the non-thrombolysis group, with an overall age range from 26 to 95 years.

We observe that among the personal pathological history of the study population, arterial hypertension was the most frequent in both groups, with a total prevalence of 63%, followed by diabetes mellitus at 26.5% and overweight/obesity at 20%. Atrial fibrillation was the least frequent, present in only 8.4% of the population.

Regarding the clinical characteristics of the population, we observed that the average time from symptom onset or from the moment the patient was found with symptoms in the case of unwitnessed stroke or wake-up stroke to the first medical attention was 956.57 min (standard deviation [SD]: 2681 min), approximately 16 h. These findings suggest the presence of multiple barriers to timely emergency care, such as symptom recognition, transportation availability, and distance to healthcare facilities. Consequently, a substantial proportion of patients in this study (n = 156) arrived beyond the therapeutic window for reperfusion therapies, which in the case of intravenous thrombolysis is limited to 270 min (4.5 h). In contrast, a smaller subset (n = 82) presented within the eligible time frame, thus qualifying for reperfusion treatment with thrombolysis and deriving subsequent benefits, including improved functional recovery and a reduced need for future medical care.

On the other hand, the average length of hospital stay was 8 days, with a maximum of 41 days. Regarding the NIHSS and mRS scores at admission, the mean values were 8 and 0 points, respectively, while at discharge, the NIHSS and mRS scores averaged 6 and 2, respectively. This indicates that the NIHSS score

Table 1. Sociodemographic characteristics of the study population

Variable	Categories	Thrombolyzed n (%)	Non-thrombolyzed n (%)	Total n	Total %
Gender	Male	47 (38.5)	75 (61.5)	122	51.3
	Female	35 (30.2)	81 (69.8)	116	48.7
Socioeconomic stratum	Stratum 0	5 (26.3)	14 (77.7)	19	8
	Stratum 1	35 (33)	71 (67)	106	44.5
	Stratum 2	42 (37.2)	71 (62.8)	113	47.5
Education	Illiterate	5 (23.8)	16 (76.2)	21	8.8
	Primary	51 (37.2)	86 (62.8)	137	57.6
	Secondy	17 (34.7)	32 (65.3)	49	20.6
	Technical	4 (50)	4 (50)	8	3.4
	Technological	0 (0)	2 (100)	2	0.8
	Universitary	3 (37.5)	5 (62.5)	8	3.4
	No data	2 (15.4)	11 (84.6)	13	5.5
Area	Urban	80 (35.1)	148 (64.9)	228	95.8
	Rural	2 (25)	3 (75)	4	1.7
Total		82	156	238	100

tended to decrease from admission to discharge in the study population, while the mRS score increased, although it still corresponds to a mild level of stroke-related disability.

In the cost calculation by groups, we observe the number of patients who received thrombolysis (n = 82) and those who received standard medical management (n = 156), with an average cost of $13,316,428.31 COP (3.269,77 USD) (SD $9,147,043/2.246 USD) for the thrombolysis group and $12,813,094 COP $12,813,094 (3.146,17 USD) (SD $12,261,577/3.010 USD) for the non-thrombolysis or standard medical management group. These direct costs include expenses related to medications, specialist consultations, rehabilitation therapies, hospital stay, and hospital supplies such as gloves, syringes, anesthesia extensions, laboratory tests, diagnostic imaging, and both invasive and non-invasive medical procedures, among others (Table 2).

In terms of disease outcomes by group, when comparing NIHSS scores at admission and discharge in the group of patients who received thrombolysis, there was a decrease of approximately 5 points, suggesting clinical improvement. On the other hand, in the group of patients who received only standard medical management, an increase in the NIHSS score at discharge compared to admission was observed.

When comparing mRS scores at admission and discharge for both groups, there was a slight increase in the score in the non-thrombolysis group, indicating greater dependence and disability at discharge in this group (Table 3).

A decision tree was used as the health economic evaluation model, outlining the two therapeutic options for patients with ischemic stroke: thrombolysis and standard medical management without thrombolysis. The NIHSS and mRS scores at discharge were considered as indicators of clinical outcomes. Subsequently, the cost was measured in COP, and effectiveness was measured in quality-adjusted life years (QALYs). Finally, a cost-effectiveness analysis was conducted using the ICER, resulting in two possible outcomes one dominated and one dominant (Fig. 1).

In addition to the decision tree, a subsequent Markov model was developed to extend the initially proposed time horizon of 3 months, considering that literature reviews indicate the most significant impact of thrombolytic therapy on disability and quality of life is more evident beyond 3 months, and even years after the event (Fig. 2).

Table 2. Total direct costs derived from medical care by groups

Variable	n	Mean (SD)	Median (IQR)	Lower limit 95% CI	Upper limit 95% CI
Thrombolyzed	82	13,316,428,31 COP (9,147,043) 3.269,77 USD (2.246 USD)	12,004,019 COP (7,041,705 COP) 2.957,33 USD (1.729 USD)	11,254,088 COP 2.763,37 USD	15,378,767 COP 3.776 USD
Non-thrombolyzed	156	12,813,094 COP (12,261,577 COP) 3.146,17 USD (3.010 USD)	8,251,604 COP (10,349,890COP) 2.026 USD (2.541 USD)	10,861,080 COP 2.666 USD	14,765,108 COP 3.625 USD
Total	238				

COP: colombian pesos; SD: standard deviation; IQR: interquartile range; CI: confidence interval.

Table 3. Disease outcome by groups in terms of severity and prognosis scales

Variable	Mean (SD)	Median (IQR)	Lower limit 95% CI	Upper limit 95% CI
Thrombolyzed				
NIHSS on Admission	10.54 (6.5)	9 (10)	9	12
NIHSS on Discharge	4.97 (7.3)	2 (5)	3.3	6.6
mRS on Admission	0.29 (0.7)	0 (0)	0.12	0.47
mRS on Discharge	2 (2)	1 (2)	1.55	2.45
Non-thrombolyzed				
NIHSS on Admission	6.8 (7.1)	4 (7)	5.7	8
NIHSS on Discharge	7.45 (9)	3 (10)	6	8.8
mRS on Admission	0.89 (1.7)	0 (1)	0.62	1.1
mRS on Discharge	2.46 (2.43)	1 (2.4)	2	2.85

SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin scale: IQR: interquartile range; CI: confidence interval.

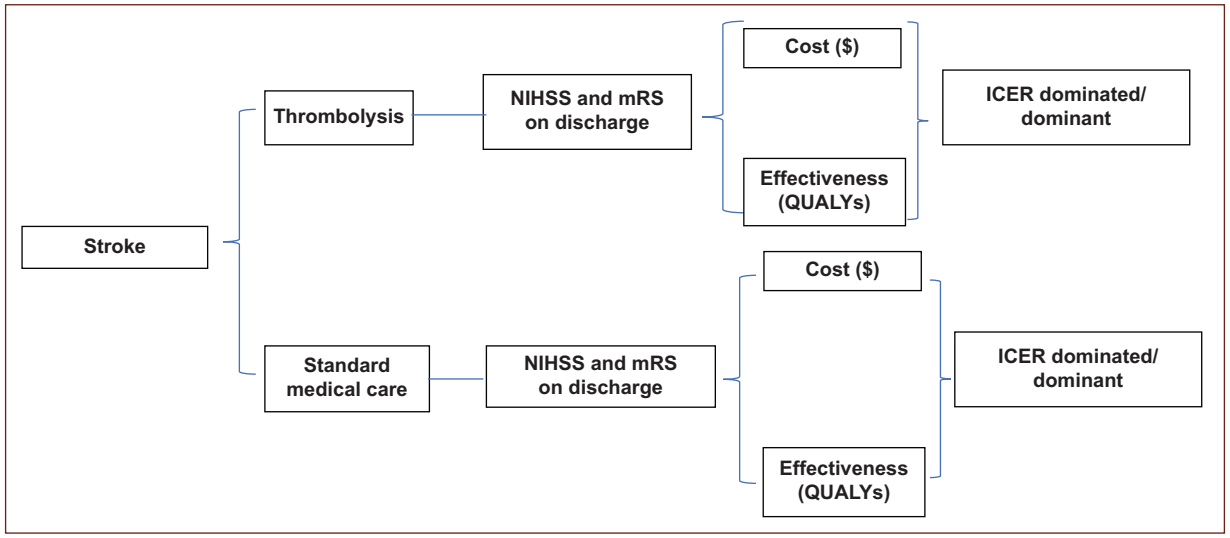

Figure 1. Decision tree. The two therapeutic options for patients with ischemic stroke are presented: thrombolysis and standard medical management without thrombolysis. The National Institutes of Health Stroke Scale and the modified Rankin scale at hospital discharge are considered as the final state for both groups, in order to later calculate costs and establish effectiveness, taking into account the incremental cost-effectiveness ratio.

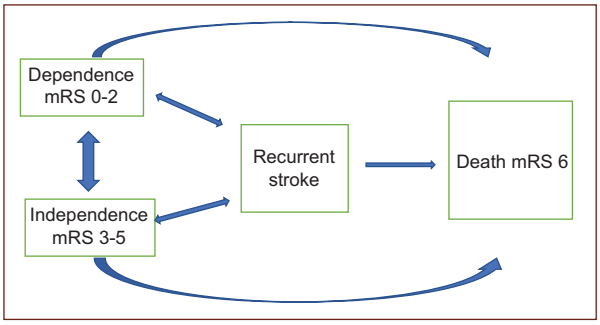

Figure 2. Markov model. The states of dependence and independence are represented according to the modified Rankin scale. The variables may be interconnected, moving from independence to dependence if the stroke recurs or from dependence to independence if the patient recovers over time. Both states – dependence and independence – can lead directly to death over time or through stroke recurrence, according to the model assumptions drawn from the literature.

In this model, we found that, when comparing the evolution of patients over time from a probabilistic perspective, about 80% of those who end up with an mRS score of 0 to 2 post-stroke would remain independent at 3 months, 2 years, and 10 years, although this may not be the case at 20 years. On the other hand, patients with an mRS score of 4 or 5 could remain in this state or progress to more severe health conditions, including death, in a shorter time.

When performing the cost-effectiveness analysis, we found that the average cost of standard medical management in the study population was $12,813,094 (3.146,17 USD), compared to $13,316,428 (3.269,77 USD) for the costs in thrombolysis patients. Regarding the evaluation of effectiveness, QALYs reported in the literature were taken into account. The data were obtained from the ECASS-3 study and from the study conducted by Tung et al.[10] In addition, the utilities and QALYs associated with the mRS scale for thrombolyzed and non-thrombolyzed patient groups were taken as a reference from international economic model studies, adapted to the Colombian population, in which the EQ-5D scale is used.[11]

The average cost-effectiveness was calculated, along with the delta for cost and effectiveness. We found that the thrombolysis group had a gain of 0.27 QALYs with a higher cost of $503,334 (123,59 USD), compared to the group that received standard medical management, with an ICER of $1,864,201 (457,74 USD) per QALY gained, a value well below the commonly accepted cost-effectiveness threshold in Colombia, indicating that thrombolysis is a highly cost-effective strategy (Table 4).

In table 5, we observe the relationship of the mRS scale at discharge with average utility values, as well as the average cost derived from the healthcare treatment of patients in both groups. In the last column, the ICER was calculated based on the mRS score and the utility measured in QALYs. We observed the mean utility values for the thrombolyzed and non-thrombolyzed groups, along with their standard deviations and p values, including 95% CIs. We found that the ICER is negative in most groups according to the mRS. In addition, we observed a mean utility of 5.9 (SD 4.7) [95% CI: 1.52-10.27; p = 0.16] for the thrombolyzed group, while for the non-thrombolyzed group, the mean was 5.35 (SD 4.6) [95% CI: 1.03-9.68; p = 0.23], neither of which was statistically significant. On the other hand, the mean delta utility was 0.54 (SD 0.28) [95% CI: 0.28-0.80; p = 0.02], which is statistically significant. Finally, the mean ICER per QALY was –1,473,833 (SD 1,656,379) [95% CI: –3,212,096 to 264,430; p = 0.81], which was not statistically significant either. The negative mean ICER suggests that thrombolysis could be a dominant strategy (more effective and less costly). However, since the confidence interval includes positive values and the result was not statistically significant (p = 0.81), the evidence remains inconclusive, and there is considerable uncertainty regarding its cost-effectiveness.

To improve the robustness of the results, a sensitivity analysis was conducted using an acceptability curve, where the available willingness to pay in COP is shown with the probability of cost-effectiveness of thrombolysis. Given that the available willingness to pay for Colombia is 17,000,000 COP per QALY gained for the year 2019[12] A sensitivity analysis was also performed to represent the incremental effectiveness in QALYs. In the following graph, we see on the Y-axis the incremental cost, with the central line representing the available willingness to pay per QALY gained. From this analysis, we see that both therapeutic strategies fall below this willingness-to-pay threshold (Fig. 3).

Discussion

There are few local studies that evaluate cost-effectiveness during the hyperacute and acute phases of ischemic stroke. The available data before this study refer to extended time horizons, and most have been conducted in developed countries. In a study conducted in the city of Medellín by Tobón-Sierra and

Table 4. Cost-effectiveness analysis – total costs by both groups

Options	Cost	Effectiveness (Tung et al.)	ACE	Delta cost	Delta effectiveness	ICER
Standard medical care	12.813.094 COP (3.146,17 USD)	6.08	2.107.416 (517,4 USD)	12.813.094 (3.146,17 USD)	6.08	2.107.416 (517,4 USD)
Thrombolysis	13.316.428,31 COP (3.269,77 USD)	6.35	2.097.075 (514,92 USD)	503.334 (123,59 USD)	0.27	1.864.201 (457,74 USD)

HACER: average cost-effectiveness; ICER: incremental cost-effectiveness ratio; COP: colombian pesos.

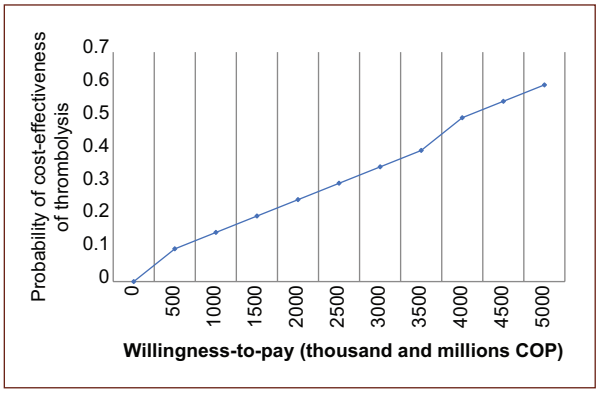

Figure 3. Acceptability curve. The X-axis shows the willingness-to-pay value in COP, while the Y-axis shows the probability of cost-effectiveness of thrombolysis. In this case, we see that the probability threshold for cost-effectiveness of thrombolysis in stroke is below the willingness-to-pay value available to the Colombian health system.

Amaya, they evaluated the cost-utility of mechanical thrombectomy alone and mechanical thrombectomy plus thrombolysis, compared with standard medical therapy. They also assessed direct costs using a 20-year time horizon and a 90 days decision tree. Their findings showed that mechanical thrombectomy combined with intravenous thrombolysis is cost-effective in the long term but not in the short term or with a time horizon shorter than 5 years.[13] These results could be extrapolated to those found in this study, where QALYs previously reported in reference studies were used as the measure of effectiveness, and real cost data from the studied healthcare provider were considered. Due to the inclusion of an expensive procedure such as mechanical thrombectomy, the results slightly differ from those obtained in this study, making it difficult to determine the cost-effectiveness of thrombolysis alone.

In the study by Tung et al., the cost-effectiveness of thrombolysis with tPA within the 3-4.5-h window was evaluated. They conducted a Markov decision model analysis to compare patients treated with tPA versus those receiving only standard medical care without tPA. A one-way sensitivity analysis and probabilistic analysis were conducted to test the robustness of the model. The results showed that tPA therapy led to a gain of 0.28 QALYs with an additional cost of $6,050 USD and an ICER of $21,978 USD per QALY. The probabilistic analysis showed an 88% probability that tPA would be the preferred treatment based on willingness to pay.[10] Although the base-case QALY values in this study were taken from Christie et al.'s publication, ICER calculations were based on real costs from the patient population treated at Kennedy Hospital. The results were similar, with a cost reduction observed in the thrombolysis group compared to the non-thrombolysis group.

Another study by Tan Tanny et al., conducted in Australia on the cost-effectiveness of thrombolysis for ischemic stroke within 4.5 h, included 378 patients who received tPA therapy. Using a 1-year time horizon, they concluded that tPA thrombolysis is cost-effective, and that the longer the time horizon, the greater the cost-effectiveness.[14]

On the other hand, in the study by Pan et al., conducted in China, which evaluated the cost-effectiveness of thrombolysis within 4.5 h of ischemic stroke, data were taken from the TIMS-China database, while effectiveness data came from the ECASS, ATLANTIS, NINDS, and EPITHET trials. They used two time horizons: 2 years and 30 years. At 2 years, the treatment with tPA showed a gain of 0.101 QALYs with an additional cost of $1,460 USD, and an ICER of $14,500 USD per QALY gained. At 30 years, there was a gain of 0.422 QALYs with an additional cost of $1,000 USD and an ICER of $2,380 USD per QALY gained.[15] The above data are consistent in showing that the longer the time horizon, the better the ICER obtained, indicating that tPA therapy remains cost-effective in terms of long-term QALY outcomes. In our study, using the actual medical

Table 5. Cost-effectiveness analysis according to mRS and healthcare costs during hospital stay

State	mRS	Thrombolyzed n	Utility QALY	Cost (COP) Mean SD	Non-thrombolyzed n	Utility QALY	Cost (COP) Mean SD	Delta utility	ICER/QALY
No symptoms	0	18	11.8	13.258.975 (3.255,66 USD) (9.038.969/2.219 USD)	46	11.4	13.082.291 (3.212 USD) (12.995.223/3.190 USD)	0,4	441.710 (108,45 USD)
No significant disability	1	29	11.3	12.973.114 (3.185 USD) (8.633.359/2.119 USD)	33	10.8	13.130.173 (3.224 USD) (12.818.884/3.147 USD)	0,5	–314.118 (–77 USD)
Mild disability	2	11	8.3	12.436.094 (3.053 USD) (8.848.314/2.172 USD)	10	7.5	13.667.886 (3.356 USD) (13.298.604/3.265 USD)	0,8	–1.539.740 (–378 USD)
Moderate disability	3	2	5.5	10.157.878 (2.494 USD) (7.635.305/1.874 USD)	16	4.8	13.159.485 (3.231 USD) (13.184.816/3.237 USD)	0.7	–4.288.010 (–1.052 USD)
Moderately severe disability	4	5	3.2	11.452.327 (2.812 USD) (8.397.990/2.062 USD)	7	2.4	13.202.856 (3.241 USD) (13.204.231/3.242 USD)	0.8	–2.188.161 (–537 USD)
Severe disability	5	7	1.2	12.772.745 (3.136 USD) (8.814.553/2.164 USD)	15	0.6	13.345.563 (3.276 USD) (13.019.922/3.196 USD)	0.6	–954.680 (–234 USD)
Death	6	9	0.00	0	25	0	0	0	

Utility QALY thrombolyzed Mean (SD)	Lower limit 95% CI	Upper limit 95% CI	p	Utility QALY non-thrombolyzed Mean (SD)	Lower limit 95% CI	Upper limit 95% CI	p	Delta utility Mean (SD)	Lower Limit 95% CI	Upper Limit 95% CI	p	ICER per QALY Mean (SD)	Lower limit 95% CI	Upper Limit 95% CI	p
5.9 (4.7)	1.52	10.27	0.16	5.35 (4.6)	1.03	9.68	0.23	0.54 (0.28)	0.28	0.80	0.02	–1,473,833 (1,656,379)	–3,212,096	264,430	0.81

mRS: modified Rankin Scale; QALYs: quality-adjusted life years, SD: standard deviation, ICER: Incremental cost-effectiveness ratio.

care costs for the population with ischemic stroke, we observed a gain of 0.27 QALYs with an additional cost of COP $503,334 compared to the group that received standard medical management, resulting in an ICER of COP $1,864,201 per QALY gained. When adjusting QALYs according to the mRS, we found a mean delta utility of 0.54 with a p-value of 0.02 for the thrombolysis group, and a negative ICER of –COP $1,473,833; thus, thrombolysis was considered a dominant alternative.

No studies were found in Latin America or Colombia that compare intravenous thrombolysis versus standard medical management in terms of cost-effectiveness. Most studies compare thrombectomy plus thrombolysis and thrombectomy alone versus thrombolysis. In a cost-utility study of endovascular therapies conducted in Chile by Lenz-Alcayaga et al., thrombectomy plus thrombolysis was compared to thrombolysis alone, from both the healthcare system and societal perspectives. They found that thrombectomy plus thrombolysis adds quality of life at acceptable costs for decision-makers compared to thrombolysis alone, which is consistent with findings from international studies.[16]

Several important limitations should be acknowledged in this study, mainly due to the lack of local data to calculate effectiveness through QALYs in the study population. Most reviewed studies use QALY values already established in large trials such as ECASS and ATLANTIS, highlighting the need for more data, especially quality related indicator for the South American region. Furthermore, evaluating long-term time horizons is challenging; most cases rely on assumptions or simulated models, where patients are presumed to be in a certain health state at a given time, using the mRS scale as the only predictive tool.

Another limitation of this study concerns the costs obtained. Ideally, indirect costs derived from the disease should also be included. However, quantifying these costs is difficult and would require analyzing a large amount of data, which often lacks exact values. A search for local literature did not yield studies evaluating indirect health care costs, so it was not possible to measure their influence on ICER variability. The direct costs obtained for this study correspond to total costs, which were used to calculate the ICER.

It is necessary to obtain local and standardized data to carry out more reproducible cost-effectiveness studies with both internal and external validity. This would improve health economic analysis studies, particularly for stroke, which is one of the main causes of morbidity, mortality, and disability.

In the future, prospective studies could be conducted using local utility data measured in QALYs from the Colombian population, and include indirect costs in addition to direct costs for a more accurate economic analysis tailored to the study population.

Conclusions

Thrombolytic therapy is associated with greater cost-effectiveness, better clinical outcomes, and reduced disability compared to standard medical management without thrombolytic therapy. The cost-effectiveness of thrombolytic therapy becomes more evident with longer time horizons. There is a preference for the use of thrombolytic therapy due to its cost, which aligns with the willingness to pay threshold per QALY in Colombia and other countries.

Hypertension was the most common preexisting condition found in the study population. Delays in the care of stroke patients persist, leading many to arrive at emergency services outside the therapeutic window for thrombolysis. This further increases disability and the loss of QALYs.

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence (AI). The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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ORIGINAL ARTICLE

Willingness to donate the brain on death for scientific research purposes in northeastern Mexico

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Abstract

Objective: *The aim of this study was to determine the willingness of inhabitants of Metropolitan Monterrey, Mexico, to donate their brains after death for scientific research purposes.* **Methods:** *An electronic survey with multiple-choice questions was administered online. Survey addresses willingness to donate their brains and the factors that may influence this decision. The survey was distributed through major social media platforms for 9 months. Percentages were calculated, and differences between groups were assessed with the χ^2 test.* **Results:** *A total of 350 people responded to the survey. Of these, 68.5% were female, 85.4% were between 18 and 39 years old, 76.2% were single or divorced, 71.1% practiced some religion, 72.9% had a bachelor's degree or higher, and 64.6% reported incomes ≤ 19,999 Mexican pesos. When asked, "How likely are you to donate your brain for scientific research after death?," 64.9% responded "highly likely" or "likely." The main reasons for donating were as follows: (1) "I like the idea that studying my brain could help save lives," and (2) "I believe I won't need my organs after death." Conversely, the main reasons for not donating were as follows: (1) "Fear that my organs might be taken prematurely when recovery is still possible," and (2) "I don't like thinking about it."* **Conclusions:** *A high proportion of Metropolitan Monterrey Mexico´s inhabitants are willing to donate their brains after death for scientific research purposes.*

Keywords: *Brain donation. Mexico. Organ donation. Monterrey.*

Disponibilidad para donar el cerebro al fallecer con fines de investigación científica en el noreste de México

Resumen

Objetivo: *Determinar la disposición de los habitantes del área Metropolitana de Monterrey, México de donar su cerebro al fallecer con fines de investigación científica.* **Métodos:** *Se aplicó una encuesta electrónica en línea con preguntas de opción múltiple, que evaluaba la disposición de donar y los factores que influyen en esta decisión. La encuesta se distribuyó durante nueve meses a través de plataformas principales de redes sociales. Se calcularon porcentajes y las diferencias entre grupos se evaluaron con la prueba de Chi-cuadrada (χ^2).* **Resultados:** *Un total de 350 personas respondieron la encuesta. De ellas, el 68.5% eran mujeres, el 85.4% tenía entre 18 y 39 años, el 76.2% eran solteros o divorciados, el 71.1% practicaba alguna religión, el 72.9% contaba con licenciatura o estudios superiores, y el 64.6% reportó ingresos ≤ $19,999 pesos mensuales. Al preguntar ¿Qué tan probable es que done su cerebro para investigación científica después de morir?, el 64.9% respondió*

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"muy probable" o "probable. " Las principales razones para donar fueron: 1) "Me gusta la idea de que estudiar mi cerebro pueda salvar vidas," 2) "Creo que no necesitaré mis órganos después de morir." Por otro lado, las razones principales para no donar fueron: 1) "Temor a que mis órganos sean extraídos prematuramente cuando aún haya posibilidad de recuperación," 2) "No me gusta pensar en ello." **Conclusiones:** *Una proporción alta de habitantes área metropolitana de Monterrey, México está dispuesta a donar su cerebro post mortem con fines de investigación científica.*

Palabras clave: *Donación de cerebro. México. Donación de órganos. Monterrey.*

Introduction

Neurological disorders are a main health challenge, with enormous economic costs. As the population grows and gets older, more people are reaching the ages at which neurological diseases are highly prevalent. In 2019, there were nearly 10 million deaths and 349 million disability-adjusted life years (DALYs) due to neurological disorders around the world. Among the 18 neurological disorders, stroke was the biggest contributor to DALYs (143232.18 in thousands) and deaths (6552.72 in thousands), followed by neonatal encephalopathy due to birth asphyxia and trauma.[1]

Studying brain disorders requires the availability of brain samples, as these can provide insights into the causes and potential treatments for such conditions. In this regard, the willingness of the population to donate their brains may positively impact neuroscience research. Since there is a lack of data in Mexico regarding the percentage of the population willing to donate their brain after death, this study aimed to determine this willingness among residents of northeastern Mexico.

Methods

Type of study

This is a cross-sectional survey study that used an electronic anonymous questionnaire.

Instrument

It was composed of two sections: the first collected sociodemographic data, and the second assessed willingness and the reasons for donating or not donating the brain.

The following question was asked to assess willingness: "How likely are you to donate your brain for research purposes after death?" Responses were recorded on a Likert scale with the following options: Highly likely, Likely, Unlikely, and I don't know. Participants were considered willing to donate if they selected "Likely" or "Highly likely." This method of assessing willingness to donate the brain has been previously reported in the literature and is commonly used in international studies on this topic (Boise et al., 2017; Sweeney et al., 2025). They were also asked to select reasons for donating or not donating based on their willingness. In the case of willingness, the options were the following; I like the idea that studying my brain could help save lives; I think I won't need my organs after I die; I think my family will find comfort knowing that studying my brain could help save lives; I prefer not to answer; and Other (unspecified). If they responded unlikely, the options were the following: Fear that my organs will be taken prematurely; I don't want my body to be disfigured; I don't like thinking about that; I prefer not to answer; I don't trust the healthcare system; I can't for medical reasons; and It goes against my religion. In addition, they were asked whether they had a relative with a brain disease.

The following sociodemographic data were collected: sex (male, female), age (Under 40 years, 40 or older), marital status (married or in a common-law union vs. single, divorced, or widowed), education (Bachelor's degree or higher vs. high school or less), household income expressed in Mexican pesos (< 10,000, 10,000-19,999, 20,000-39,999, > 40,000), and if they practice any religion (yes vs. no).

Data collection

The survey was conducted online and disseminated freely through various electronic media and social networks, mainly Facebook and Instagram. Only individuals over 18 years of age were invited to participate in the survey. A convenience sample was used in this study, with data collection limited to a specific period, from February to October 2024.

Statistical analysis

Response frequencies were calculated as appropriate. Differences among the studied groups were

Table 1. Willingness to donate the brain for research purposes (%)

Variable	Highly likely or likely	Do not know	Unlikely
Total (n = 350)	64.9	17.7	17.4
Sex			
Female (n = 110)	66.4	17.3	16.3
Male (n = 240)	64.2	17.9	17.9
p	0.91		
Age			
under < 40 years old (n = 299)	68.2	16.4	15.4
40 years or older (n = 51)	45.1	25.5	29.4
p	< 0.01		
Marital status			
Married or common-law marriage (n = 83)	49.4	22.9	27.7
Single, divorced, widowed (n = 267)	69.7	16.1	14.2
p	< 0.05		
Education			
Bachelor or higher (n = 255)	63.9	16.9	19.2
High school or les (n = 95)	67.4	12.6	20.0
p	0.33		
Home incomes			
< 10000 mx (n = 109)	67.9	18.3	13.8
10 a 19999 mx (n = 117)	69.2	16.3	14.5
20 a 39999 mx (n = 81)	56.8	21.0	22.2
> 40000 mx (n = 43)	60.5	11.6	27.9
p	0.23		
Practice any religion			
Yes (n = 249)	61.9	20.5	17.7
No (n = 101)	71.3	10.9	17.7
p	0.09		
Have a family with any brain disease			
Yes (n = 77)	76.6	14.3	9.1
No (n = 264)	62.5	17.4	20.1
p	0.04		

assessed using the χ^2 test. All analyses were performed using the NCSS12 statistical software package. The Institutional Board Review approved this study.

Results

A total of 350 people responded to the survey. The main sociodemographic characteristics are as follows: 68.6% were female, 85.4% were under 40 years old, 76.3% were single/divorced/widowed, 71.1% practiced a religion, 72.9% had at least a bachelor's degree, and 64.6% reported household incomes below 20,000 Mexican pesos (approximately USD 1,100).

About 64.9% of respondents indicated a willingness to donate their brains for research purposes after dying. Significant between-group differences were observed in three groups: (1) marital status – single/divorced participants demonstrated greater willingness (69.7%, $p < 0.05$); (2) age – individuals under 40 years showed higher disposition (68.2%, $p < 0.05$); and (3) family history – respondents with affected relatives reported the highest willingness (76.6%, $p < 0.01$). The rest of the groups studied did not show statistically significant differences in the willingness to donate their brains (Table 1).

The three main reasons for donating the brain were: (1) liking the idea that studying their brain could help save lives, (2) believing they wouldn't need their organs after death, and (3) thinking their family would find comfort knowing the brain study might save lives (Fig. 1A). On the other hand, the three main reasons for not donating the brain were as follows: (1) fear of organs being taken prematurely when recovery was still possible, (2) not wanting their body to be cut or disfigured, and (3) not liking to think about it (Fig. 1B).

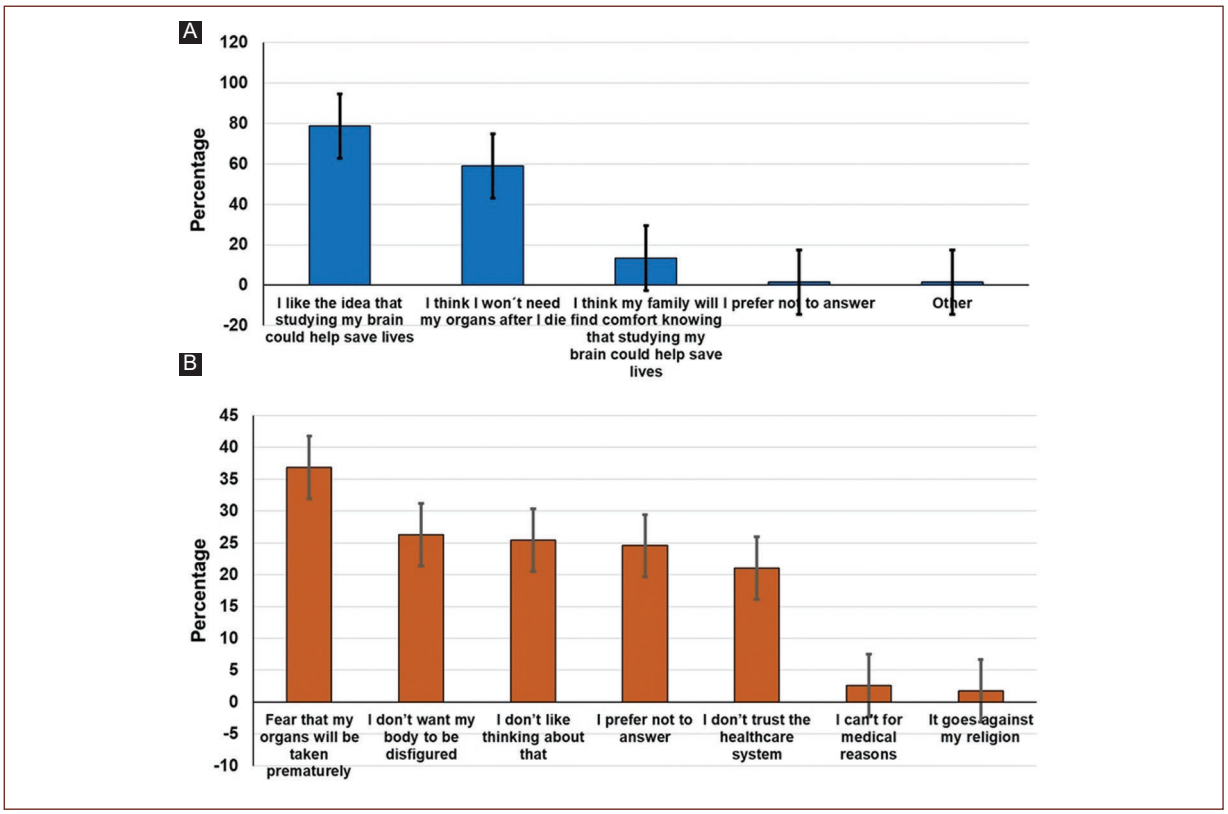

Figure 1. Motivations for (A) donate (B) do not donate the brain for research purposes.

Discussion

This is the first study to analyze the willingness to donate the brain after death in a sample of inhabitants of Metropolitan Monterrey, Mexico. Most previous studies have focused on unspecified organ or tissue donation for transplantation, where the willingness to donate ranges between 70.0% and 80.0%.[2,3]

The results of this study show that a high proportion of participants (64.9%) are willing to donate the brain for research purposes; however, this value is less than that for organ transplantation. These findings are similar to those reported in the USA (64.0%),[4] lower than in Australia (84.0%),[5] and higher than in Nigeria (26.7%),[6] and China (26.4%).[7] This variation strongly suggests that a combination of cultural, religious, educational, and psychological factors contributes to the willingness to donate the brain.

In the present study, single or divorced individuals, those under 40 years of age, and respondents with a relative who had a neurological disease were the groups that reported higher percentages of willingness to donate the brain. Previous studies have identified several factors contributing to variations in willingness to donate the brain, some of which are contradictory. These include sociodemographic factors such as gender, age, education level, having a neurological disease, or having a relative with one. Religious beliefs, such as views about the body after death, and cultural aspects, including distrust in the healthcare system, also play a role. In addition, the idea that brain donation is invasive or disfiguring can create emotional discomfort.[7-11]

The main motivation for donating the brain in the present study was altruistic, "the idea that studying their brain could help save lives," which is consistent with previous reports.[10] This altruistic motivation may help patients and families make sense of the death and foster healthy bereavement.

Although most individuals surveyed report a willingness to donate the brain, some authors suggest that many people have difficulty with the concept of "donation for research".[11] Therefore, it is important to disseminate more information to the public so that this concept becomes widely accepted in Mexico. As the general public's knowledge increases, the willingness to donate the brain will also increase.

Willingness does not necessarily imply an intention to donate the brain, so this aspect merits research. Despite several studies, including this one, which show that the population expresses interest in brain donation, the actual donation rate remains low, ranging from 5% to 43%.[5,12]

Some limitations of this study should be considered for a better interpretation of the findings. Since the survey was freely disseminated through electronic media, it was not possible to determine the response rate. Young people are more familiar with electronic media and social networks; therefore, the sample may be biased toward young individuals, and the results may not be generalizable to older individuals or those with limited resources, such as a lack of access to the internet or mobile devices.

In addition, the results regarding willingness to donate the brain may not be extrapolated to all inhabitants of Mexico, as the Metropolitan area of Monterrey has different characteristics compared to other regions of the country.

Conclusion

A high proportion of inhabitants of Metropolitan Monterrey, Mexico, are willing to donate the brain after death for research purposes. Willingness is significantly higher among (1) individuals under 40-years-old, (2) single/divorced/widowed persons, and (3) those with relatives affected by brain diseases.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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

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REVIEW ARTICLE

The multiple faces of dementia: a study of Alzheimer's, vascular dementia, and frontotemporal dementia

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Abstract

This narrative review explores dementia, a multifaceted clinical syndrome of neurodegenerative or vascular origin characterized by progressive cognitive decline affecting autonomy and quality of life. Given its rising global prevalence, particularly in developing countries, and the absence of a curative treatment, understanding this condition is of paramount importance. A structured but non-systematic search was conducted in PubMed, Scopus, and ScienceDirect for studies published between 2015 and 2025, focusing on systematic reviews, meta-analyses, clinical guidelines, and original research in English or Spanish. After applying inclusion and exclusion criteria, 50 high-quality studies were included. This review addresses key aspects, including modifiable and non-modifiable risk factors such as education, physical inactivity, hypertension, and pollution, as well as associated pathologies such as type 2 diabetes and traumatic brain injury. It delves into the distinct characteristics, pathophysiology, and clinical stages of Alzheimer's disease, vascular dementia, and frontotemporal dementia. This document also discusses diagnostic challenges and current symptomatic treatment approaches, emphasizing the critical role of prevention and early non-pharmacological interventions to improve patient outcomes and quality of life.

Keywords: *Dementia. Alzheimer's disease. Vascular dementia. Frontotemporal dementia. Dementia risk factors.*

Las múltiples caras de la demencia: un estudio de la demencia de Alzheimer, la demencia vascular y la demencia frontotemporal

Resumen

Esta revisión narrativa explora la demencia, un síndrome clínico multifacético de origen neurodegenerativo o vascular, caracterizado por un deterioro cognitivo progresivo que afecta la autonomía y la calidad de vida. Dada su creciente prevalencia mundial, especialmente en los países en desarrollo, y la ausencia de un tratamiento curativo, comprender esta condición resulta de suma importancia. Se realizó una búsqueda estructurada pero no sistemática en las bases de datos PubMed, Scopus y ScienceDirect, para identificar estudios publicados entre 2015 y 2025, con énfasis en revisiones sistemáticas, metaanálisis, guías clínicas y artículos originales en inglés o español. Tras aplicar los criterios de inclusión y exclusión, se incluyeron 50 estudios de alta calidad. Esta revisión aborda aspectos clave, entre ellos los factores de riesgo modificables y no modificables, como el nivel educativo, la inactividad física, la hipertensión arterial y la contaminación ambiental, así

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como patologías asociadas como la diabetes mellitus tipo 2 y el traumatismo craneoencefálico. Asimismo, analiza las características distintivas, la fisiopatología y las etapas clínicas de la enfermedad de Alzheimer, la demencia vascular y la demencia frontotemporal. Finalmente, se discuten los desafíos diagnósticos y los enfoques actuales de tratamiento sintomático, destacando el papel crítico de la prevención y de las intervenciones no farmacológicas tempranas para mejorar los resultados clínicos y la calidad de vida de los pacientes.

Palabras clave: *Demencia. Enfermedad de Alzheimer. Demencia vascular. Demencia frontotemporal. Factores de riesgo de demencia.*

Introduction

Dementia is a clinical syndrome of neurodegenerative or vascular origin, characterized by a progressive decline in cognitive functions that affect the autonomy and quality of life of those who suffer from it. Among its most common forms are Alzheimer's disease (AD), which is marked by memory loss and progressive disorientation; vascular dementia, associated with cerebrovascular events that impair executive function; and frontotemporal dementia, in which behavioral and language disturbances predominate.[1,2]

According to the World Health Organization (WHO) and the 2024 Lancet Commission on Dementia Prevention, Intervention, and Care, dementia currently affects more than 55 million people worldwide, with nearly 10 million new cases each year. Approximately 60-65% of those living with dementia reside in low-and middle-income countries (LMICs), where rapid population aging, limited healthcare access, and high prevalence of vascular and metabolic disorders amplify the disease burden.[3,4] The global number of individuals with dementia is projected to triple by 2050, reaching over 150 million cases, largely driven by demographic transitions and longer life expectancy.[3,4] These trends underscore dementia as one of the leading causes of disability and dependency among older adults, representing a growing socioeconomic and public health challenge worldwide.[3,4]

Among its most common forms are AD, characterized by progressive memory loss and disorientation; vascular dementia, resulting from cerebrovascular injury and executive dysfunction; and frontotemporal dementia, marked by behavioral and language disturbances.[5-7]

Once prodromal symptoms appear or the disease becomes evident, the neurological damage already in place cannot be reversed.[4,5,8] To date, no curative treatment is available to stop or reverse cognitive decline, regardless of the type of dementia.[4,8] However, it has been clearly established that there are various risk factors that predispose individuals to the development of this disease. A considerable proportion of these risk factors is modifiable, meaning that they can be addressed through lifestyle changes, especially if targeted during midlife.[2,3,9] This highlights the importance of prevention as a fundamental public health strategy: even in the absence of a curative treatment, adopting preventive measures can significantly reduce the likelihood of developing dementia. In contrast, there are also non-modifiable factors, determined from birth, such as genetic predisposition, ethnic background, or socioeconomic status, which also influence an individual's vulnerability to this disorder.[1-3]

Various studies, including systematic reviews and meta-analyses, have identified different modifiable factors associated with the development of dementia in different populations. These include inadequate education, untreated hearing loss, uncontrolled high blood pressure, overweight, tobacco use, depression, physical inactivity, diabetes, excessive alcohol consumption, traumatic brain injuries, exposure to environmental pollution, social isolation, vision loss, and high levels of LDL cholesterol. Many of these factors are closely related and tend to coexist in developing countries.[2,3,9-16] For example, in the case of Mexico, a significant prevalence of several of these risk factors is observed.[3,9,17] The population's average level of education is relatively low, which limits the development of a proper cognitive reserve to cope with the effects of brain aging. In addition, conditions such as hypertension, overweight, smoking, physical inactivity, alcohol abuse, and exposure to high levels of air pollution are common in the Mexican population, which significantly increases the risk of developing dementia in old age[3].[1,2]

Materials and methods

This work constitutes a narrative review, designed to synthesize and critically analyze recent scientific literature on AD, vascular dementia (VaD), and frontotemporal dementia (FTD). The review aimed to identify current evidence on their epidemiology,

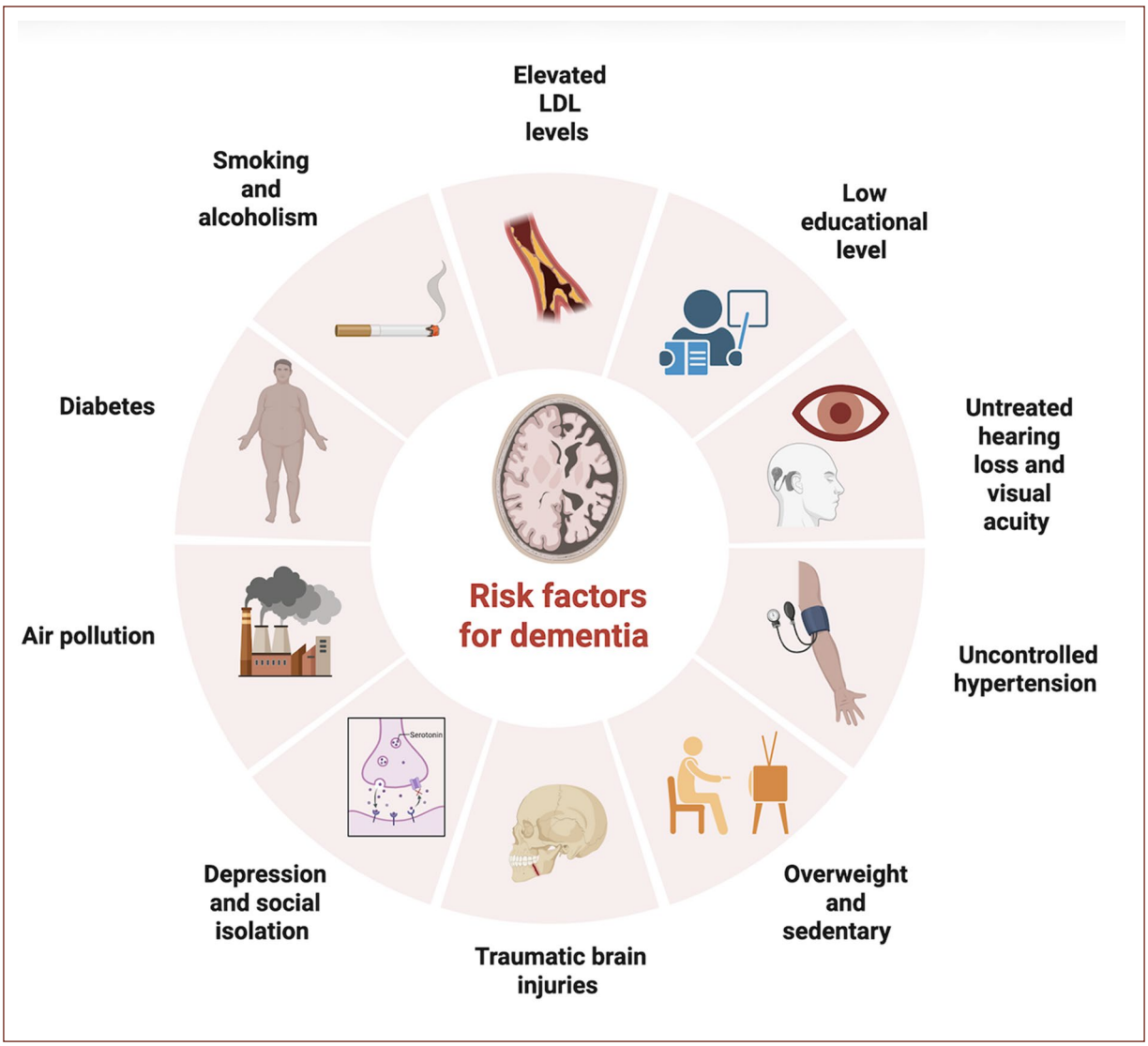

Figure 1. Risk factors for dementia.

pathophysiology, risk factors, diagnostic approaches, and management strategies.

A structured but non-systematic search was conducted across the following electronic databases: PubMed/MEDLINE, Scopus, and ScienceDirect.

The search covered publications from January 1, 2015, to April 30, 2025, using the following keywords: ("Alzheimer's disease" OR "vascular dementia" OR "frontotemporal dementia") AND ("risk factors" OR "pathophysiology" OR "diagnosis" OR "management" OR "treatment" OR "cognitive decline"). Equivalent terms were also searched in Spanish (e.g., demencia de Alzheimer, demencia vascular, demencia frontotemporal).

The search was limited to studies published in English or Spanish and indexed in peer-reviewed journals. Titles and abstracts were screened manually to identify studies relevant to dementia subtypes and their risk determinants. The following inclusion criteria were applied:

- Publications from 2015 to 2025 (to ensure contemporary evidence)
- Systematic reviews, meta-analyses, clinical guidelines, or original research with robust methodology
- Studies addressing human populations.

Exclusion criteria included:

- Duplicated entries
- Studies with outdated or non-reproducible data

– Case reports, editorials, opinion pieces, or letters without empirical data.

Priority was given to:

– Systematic reviews and meta-analyses (highest level of evidence)
– Clinical practice guidelines issued by recognized organizations (e.g., WHO, NICE, and ADA)
– Large-scale cohort or epidemiological studies offering relevant population-level insights.

Given the narrative nature of this review, data extraction was qualitative and descriptive. No quantitative synthesis, meta-analysis, or statistical pooling was performed. Findings were grouped thematically into categories: modifiable risk factors, comorbidities, and disease-specific mechanisms (for AD, VaD, and FTD).

Claims of association are presented cautiously, emphasizing correlation rather than causation where experimental evidence is lacking.

Results

A total of 734 articles were initially identified through the database search using the predefined keywords. After removing duplicates (n = 212) and excluding studies that did not meet the inclusion criteria (n = 472) such as those with outdated data, small or unrepresentative samples, or limited methodological rigor, 50 articles were finally included in this narrative review. These comprised systematic reviews, meta-analyses, clinical guidelines, and original studies relevant to the epidemiology, pathophysiology, risk factors, and treatment of dementia.

Main risk factors

A significant proportion of these modifiable factors is also associated with the development of cardiovascular diseases.[9] In this regard, the study developed by Liv Tybjærg and collaborators revealed a strong relationship between elevated body mass index (BMI) and other conditions such as physical inactivity, dyslipidemia, diabetes, hypertension, and smoking.[9] According to the *2024 Lancet Commission*, managing these modifiable risk factors could prevent or delay up to 40% of dementia cases globally.[3] These factors are major contributors to the development of atherosclerosis, a condition characterized by partial obstruction of the arteries. The reduced blood flow caused by this condition leads to hypoxia in the brain's capillary network, promoting neuronal death and thereby contributing to the development of dementia.[9]

Education and isolation

Among the lifestyle-related factors, education stands out as one of the most relevant. Evidence indicates that limited academic education is associated with a lower cognitive reserve, which is a reduced ability of the brain to compensate for neurodegenerative damage.[10] This effect strengthens in contexts of social isolation, as maintaining close interpersonal relationships and an active support network is positively correlated with better cognitive performance.[11] Likewise, isolation has been shown to disrupt the hypothalamic-pituitary-adrenal axis, affecting cortisol release and contributing to chronic physiological imbalance.[11] This effect is particularly notable in women, who tend to receive less social support and may therefore be more vulnerable to cognitive decline.[11] In parallel, depression represents a significant risk factor, as it negatively impacts neuroplasticity and encourages harmful lifestyle habits such as sedentarism and social withdrawal, further reducing cognitive reserve and promoting the development of neurological disorders.[2,3,10,11]

Sedentary lifestyle

Prolonged sedentary behavior – particularly sitting for ≥ 10 h/day – has been linked to higher dementia risk, possibly through impaired cerebral perfusion and neuroplasticity.[12] Physical inactivity, present in more than 50% of the older adult population, has been linked to reduced cerebral blood flow.[12] Recent research indicates that spending more than 10 h a day in a sedentary state significantly increases the risk of developing dementia.[12] In contrast, regular physical activity – at least 150 min/week of moderate exercise, as recommended by the American Diabetes Association – enhances neuroplasticity and reduces that risk.[12,18] Sedentary behavior also tends to coexist with overweight and elevated BMI, which induces chronic inflammation and insulin resistance – processes associated with reduced brain volume and deterioration of neural connections.

BMI

It is worth noting that an excessively low BMI – typically between 18.5 and 22.4 kg/m^2 – has also been linked to an increased risk of non-vascular dementias in older adults.[13] However, this association appears to be influenced by reverse causality, as early or prodromal stages of dementia can lead to unintentional weight

loss before a formal diagnosis. The relationship between a low BMI and dementia may actually reflect the subclinical expression of prodromal cognitive decline, rather than a causal effect of low weight itself.[13] This interpretation highlights the importance of distinguishing vascular from non-vascular mechanisms when evaluating metabolic predictors of dementia risk in aging populations.[9,12,13]

Cholesterol imbalance

On the other hand, high levels of LDL cholesterol compromise the integrity of the blood-brain barrier, alter cerebral perfusion, and promote the accumulation of neurotoxic proteins such as α-synuclein, contributing to the pathophysiology of various neurodegenerative diseases.[13,17]

Tobacco and alcohol consumption

Tobacco consumption constitutes a key link in the chain of risk factors, as it induces oxidative stress in brain tissue and reduces levels of endogenous antioxidants.[14] These effects are associated with increased vulnerability to neurological deterioration, especially when smoking starts at an early age. Moreover, tobacco use is closely related to the onset of cardiovascular diseases, high blood pressure, and atherosclerosis. According to estimates by *The Lancet*, smoking cessation can reduce the risk of dementia by up to 8%.[14]

Similarly, chronic and excessive alcohol consumption has been shown to accelerate brain aging, reflected in a decrease in gray matter observed in neuroimaging studies, even in individuals who stopped drinking decades before being diagnosed.[3,15]

Air pollution

Air pollution constitutes a significant but often underestimated environmental risk factor for dementia.[16] Epidemiological studies have demonstrated that prolonged exposure to fine particulate matter ($PM_{2.5}$; particles ≤ 2.5 μm in diameter) is strongly associated with neuroinflammation, oxidative stress, and accelerated cognitive decline.[16] The BMJ meta-analysis (Wilker et al., 2023) identified a consistent relationship between $PM_{2.5}$ exposure and higher incidence of Alzheimer's and non-vascular dementias, particularly in urban populations. In addition to fine particles, nitrogen dioxide (NO_2) and nitric oxide (NO) – gaseous pollutants derived mainly from vehicle emissions and industrial combustion – have also been linked to an elevated risk of dementia due to their ability to penetrate the blood-brain barrier, induce endothelial dysfunction, and promote amyloid-β aggregation.[16] Collectively, these findings highlight that airborne particulate and gaseous pollutants act synergistically to impair cerebral perfusion and accelerate neurodegenerative processes, underscoring the need for stricter environmental health regulations in dementia prevention.[16]

Pathologies associated with cognitive decline

Hypertension (HTN) reduces cerebral blood flow, damages the vasculature, and is associated with vascular dementia. Medications such as calcium channel blockers and angiotensin receptor blockers (ARBs) could mitigate this risk.[9] However, some studies have questioned their efficacy compared to placebo, yielding inconsistent results.[19]

Hearing loss, especially in patients over 60, affects brain structures like the hippocampus and reduces cognitive reserve.[20] The use of hearing aids can partially reverse this effect by stimulating the development of affected cortical areas and slowing the progression of decline, demonstrating that early interventions are crucial.[20] Similarly, loss of visual acuity forces the brain to reallocate cognitive resources to compensate for the sensory deficiency, which accelerates cognitive decline and may coexist with depression or social isolation.[21]

Type 2 diabetes mellitus (T2DM) is a major metabolic disorder that significantly increases the risk of cognitive decline and dementia.[22] This association is primarily mediated by insulin resistance in the brain, which alters neuronal energy metabolism and promotes oxidative stress and chronic inflammation, leading to synaptic dysfunction and accelerated neurodegeneration.[22] Insulin signaling plays a crucial role in neuronal survival, plasticity, and glucose utilization; its disruption reduces brain glucose uptake and contributes to deficits in memory, attention, and executive function.[22]

Finally, moderate to severe traumatic brain injury (TBI) triggers neurodegenerative cascades: it damages white matter, induces inflammation, and promotes the accumulation of tau and beta-amyloid proteins.[23-25] Patients aged 50-69 with a history of TBI have a 30% higher risk of developing dementia, underscoring the need for prolonged neurological monitoring.[24,25]

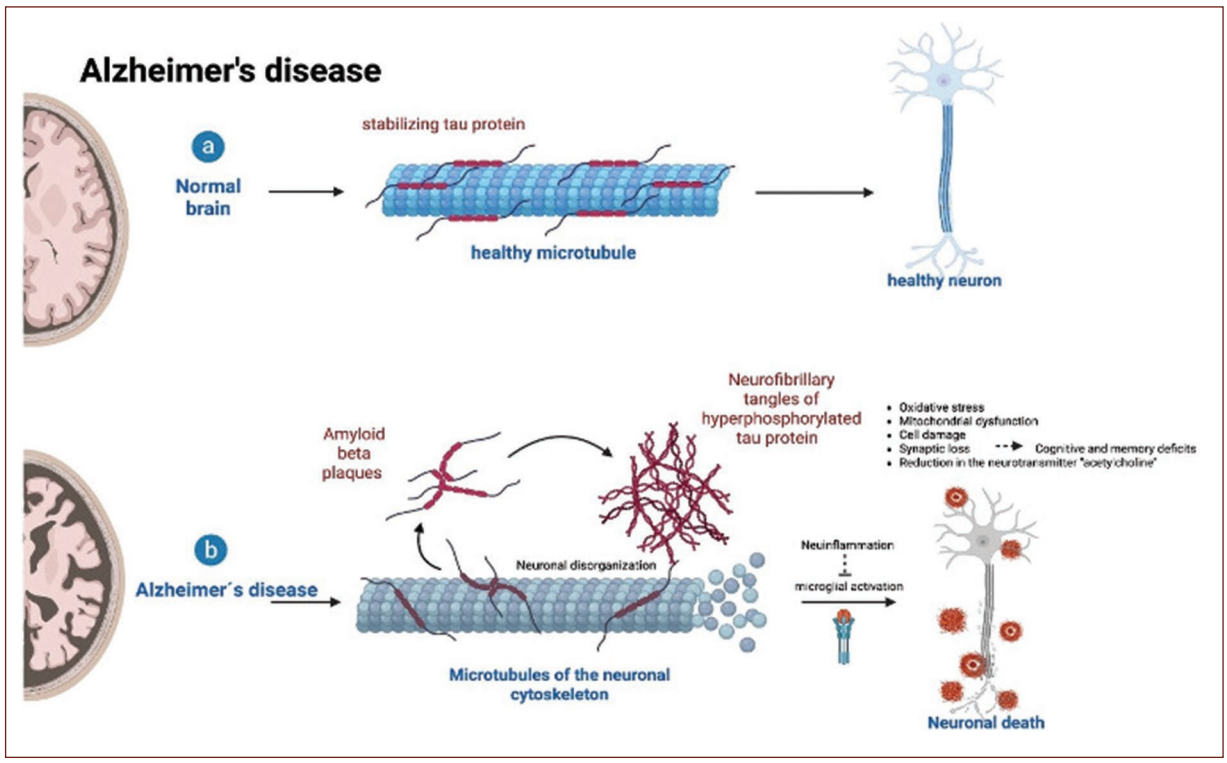

Figure 2. Pathophysiology of AD.

AD

AD is a progressive neurodegenerative disorder and the most common form of dementia. Clinically, it is characterized by the deterioration of memory, thinking, language, and problem-solving abilities.[5] The WHO has classified it as a public health priority due to its high fatality rate, economic cost, and associated disability.[4,8]

In 2018, AD International estimated that around 50 million people were living with dementia worldwide, with projections suggesting this number will triple by 2050, especially in LMICs.[4] According to the WHO, more than 55 million people currently suffer from dementia, and over 60% of them live in developing countries. However, a slight decline in incidence has been observed in high-income countries.[4]

The main risk factor for the development of AD is aging.[4,5,8] Prevalence increases from 5% to 8% in individuals over 65 years to 25-50% in those over 85 years old.[8] Nonetheless, both dementia and AD remain underdiagnosed globally, and in many cases, the diagnosis is made at late stages, making treatment and prevention more difficult. Lack of awareness contributes to stigmatization and creates barriers to timely diagnosis.[4]

AD is more common in women. Its prevalence is 19-29% lower in men.[5] A study conducted in the U.S. found an average post-diagnosis survival time of 3-4 years.[4]

Cognitive decline in AD is associated with the accumulation of toxic protein fragments, such as amyloid plaques (β-amyloid) and neurofibrillary tangles (hyperphosphorylated tau), along with progressive synaptic loss.[4,8,26] Although β-amyloid plaques and neurofibrillary tangles have traditionally been regarded as the principal drivers of neurodegeneration, recent research highlights that their formation is influenced by metal dyshomeostasis – particularly involving iron, copper, and zinc – which contributes to oxidative stress and exacerbates neuronal injury.[27] Part of the pathophysiology is illustrated in figure 2.[4,8,27]

Although Aβ plaques and tau neurofibrillary tangles have long been considered the primary neuropathological hallmarks of AD, their causal role remains debated.[4,8] Some studies propose that Aβ and tau aggregation may represent downstream consequences of broader neurodegenerative cascades, rather than the initiating events of neuronal death.[27] Current consensus acknowledges that these proteins are central but not exclusive drivers of disease pathology,

integrating with metabolic, vascular, and immune pathways.[28,29]

At present, research has shifted toward a more cellular approach, incorporating the study of other cell populations in addition to neurons. Among the multifactorial pathways involved in AD are vascular abnormalities, oxidative stress, mitochondrial changes, neuroinflammation, and reduced brain glucose metabolism.[26]

Particularly, microglia have gained attention. Under normal conditions, these cells play a role in immune surveillance and synaptic remodeling. However, in AD, their chronic and dysfunctional activation leads to neuroinflammation and neuronal death.[28] In the early stages, microglia display a neuroprotective profile, but in later stages, they adopt a pro-inflammatory phenotype that exacerbates damage. Excessive activation of the NLRP3 inflammasome has been linked to tau spreading and the worsening of amyloid pathology.[29]

Many risk genes for AD, such as *PSEN1*, *PSEN2*, *APP*, *SORL1*, *TREM2*, and *ABCA7*, are related to microglial functions.[4,27-29] Mutations in TREM2, for example, have been associated with a significant increase in the risk of developing the disease. These findings reinforce the central role of microglia in the pathogenesis of AD.[29,30]

Once the nervous system loses the ability to compensate for neuronal damage, AD clinically manifests. Its clinical phenotypes include amnesic forms (with early memory loss) and non-amnesic forms (which are rarer), with expression varying according to the age of onset.[30]

Four clinical stages of AD are currently recognized:

1. Preclinical stage: mild memory loss and neuropathological changes, with no functional impairment or evident clinical symptoms.[31]
2. Mild stage: onset of symptoms, difficulties in daily activities, disorientation, mood changes, and depression.[31]
3. Moderate stage: progressive memory loss, difficulty recognizing people, emotional and language disturbances.[31]
4. Severe stage: diffuse cortical involvement, complete loss of cognitive functions, debilitation, difficulty swallowing, and risk of death from associated complications.[31]

The current understanding of AD has shifted from a purely clinical to a biological definition, as proposed by the 2023 NIA-AA (National Institute on Aging-Alzheimer's Association) framework, which conceptualizes AD based on the AT(N) classification system:[26]

- A (Amyloid pathology) measured by decreased CSF Aβ42/40 ratio or positive amyloid positron emission tomography (PET) uptake
- T (Tau pathology) assessed by elevated CSF phosphorylated tau (p-tau181, p-tau217, or p-tau231) or tau PET imaging
- N (Neurodegeneration) indicated by increased CSF total tau (t-tau), hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), or cortical atrophy on magnetic resonance imaging (MRI).

Recent advances in blood-based biomarkers – including plasma p-tau217, p-tau231, and Aβ42/40 ratio – offer promising non-invasive alternatives for early detection, with diagnostic accuracies approaching that of CSF measures.

This biologically grounded framework enables a continuum-based diagnosis encompassing preclinical, prodromal, and dementia stages of AD, supporting personalized prognostic and therapeutic strategies. Integration of AT(N) biomarkers is now recommended in clinical trials and, when feasible, in specialized diagnostic settings.[4,26]

Vascular dementia

Vascular dementia (VaD) is a neurological disorder characterized by progressive cognitive impairment that affects various higher mental functions, such as memory, attention, and executive function. Unlike other forms of dementia, VaD is directly associated with vascular lesions in the central nervous system, highlighting its origin in disturbances in cerebral blood flow. These disturbances result in an inadequate supply of oxygen and nutrients to the neurons, thereby compromising their integrity and function.[6] The underlying causes can be acute, such as strokes (CVA), or chronic, such as the changes associated with aging, which affect the body's ability to maintain homeostasis and carry out tissue repair processes.[32]

One of the most accepted pathophysiological hypotheses today is that of chronic cerebral hypoperfusion (CCH), which represents a convergence point for various pathological mechanisms – including oxidative stress, persistent inflammation, progressive neurodegeneration, and brain atrophy – which together contribute to the onset and perpetuation of the cognitive damage characteristic of this condition.[33] The term "vascular dementia" thus refers to a causal relationship between cognitive decline and a clearly identifiable vascular etiology. The most common causes include

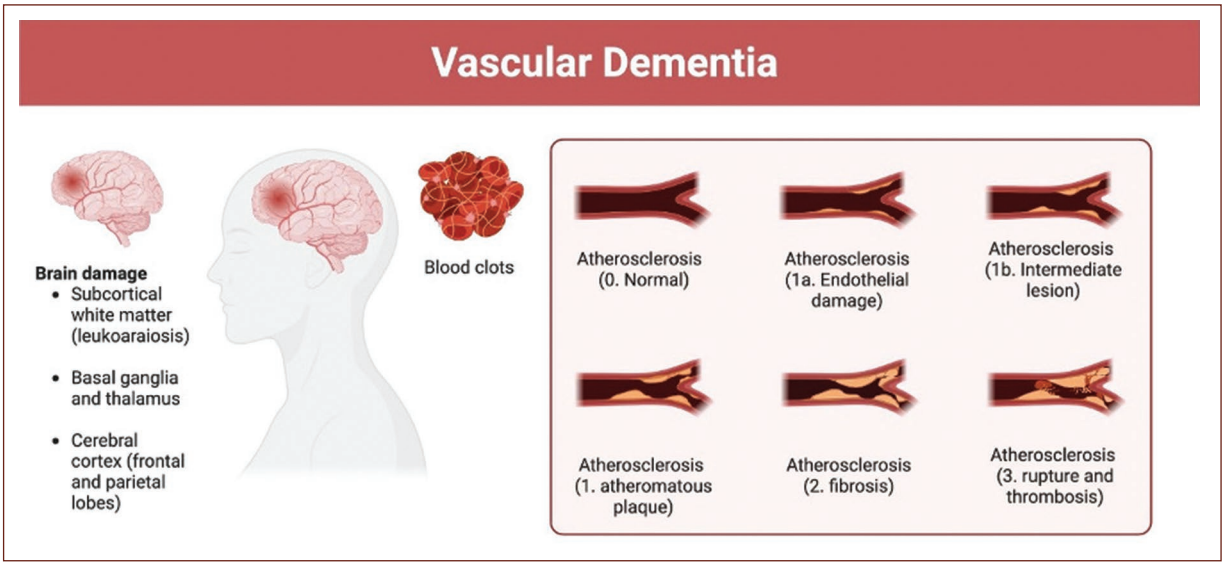

Figure 3. Atherosclerosis and VaD.[33,35,40,41]

cerebral infarctions of various magnitudes, cerebral hypoxia secondary to cardiovascular pathologies, intracranial hemorrhagic events, and the degenerative changes associated with aging, all of which can induce progressive neuronal damage.[34]

In recent years, the concept of vascular cognitive dysfunction (VCD) has gained prominence, emphasizing the role of cerebral vascular alterations as the etiological substrate of cognitive decline.[35] This term encompasses a broader spectrum of clinical severity, ranging from mild cognitive impairment to advanced forms of dementia.[36] While VaD and VCD are often used together, they are not strict synonyms: while VaD represents an advanced and well-defined form within this continuum, VCD also includes more subtle presentations attributed to underlying vascular damage.[37]

From an epidemiological perspective, vascular dementia (VaD) is the second most frequent cause of dementia worldwide, only preceded by AD. It is estimated to account for between 15% and 20% of cases in regions such as North America and Europe,[38] although in some populations, this figure can rise to as much as 30%. Recent studies suggest a possible decrease in its prevalence in countries with efficient healthcare systems, attributable to better control of risk factors such as hypertension and T2DM.[39] However, in developing countries, including Mexico, the disease burden continues to rise, partly due to limitations in access to and adherence to treatments for chronic diseases. The incidence of VaD increases exponentially with age, affecting approximately 6% of people between 75 and 79 years old, 18.3% between 85 and 89 years old, and reaching up to 41.1% in individuals over 95 years old.[40]

Among the identified risk factors, some are non-modifiable, such as male sex, family history of VaD, and genetic predisposition. Others, however, can be addressed through primary and secondary prevention strategies: hypertension, T2DM, cardiovascular diseases, dyslipidemia, and smoking represent modifiable factors with a high clinical impact.[39] Timely identification and management of these determinants are key elements in reducing the likelihood of development and slowing the progression of VaD.[39,40]

From a pathophysiological perspective, VaD and VCD share a complex and multifactorial etiology, where cerebral vascular damage leads to neuronal dysfunction. In most cases, this damage is related to processes of arteriosclerosis and atherosclerosis (Fig. 3),[33,35,40,41] which decrease cerebral blood flow and predispose to ischemic events.[34] These processes contribute to the formation of cortical microinfarcts, microscopic lesions that, although clinically unnoticed in isolation, lead to progressive deterioration of neuronal connectivity when they occur cumulatively.[34,40,42]

Vascular dementia (VaD) encompasses cognitive impairment secondary to cerebrovascular disease, most often due to cerebral small-vessel disease (CSVD), ischemic infarcts, or hypoperfusion-related

Table 1. Different clinical features and its genetic association in FTD[7,44,45,47,48]

Variant	Main clinical features	Neuroimaging findings	Genetic associations
Behavioral variant	Disinhibition, apathy, loss of empathy, stereotyped behavior, poor judgment	MRI: frontal±anterior temporal atrophy; PET: hypometabolism in frontal regions	C9orf72, GRN
Semantic variant primary progressive aphasia	Loss of word meaning, anomia, prosopagnosia, surface dyslexia	MRI: left anterior temporal atrophy; PET: hypometabolism in the temporal pole	MAPT, occasionally GRN
Non-fluent/agrammatic variant	Effortful, halting speech, agrammatism, speech apraxia	MRI: left inferior frontal gyrus and insula atrophy; PET: hypometabolism in the same areas	MAPT, C9orf72
FTD with motor neuron disease	Behavioral or language symptoms + motor weakness, fasciculations, spasticity	MRI: diffuse frontotemporal atrophy	C9orf72 (most frequent)

Tau PET imaging shows limited diagnostic utility in FTD, as most subtypes exhibit off-target binding or absent tracer uptake, restricting its application to research settings. PET: positron emission tomography; MRI: magnetic resonance imaging; FTD: frontotemporal dementia.

injury.[6,33,34] Diagnostic frameworks such as vascular cognitive impairment harmonization standards (VASCOG) and vascular impairment of cognition classification (VICC) provide standardized criteria integrating clinical, imaging, and neuropathological findings.[35,36]

In addition, other mechanisms have been identified, such as dysfunction of the blood-brain barrier – which allows neurotoxic substances to enter the brain parenchyma – and chronic neurovascular inflammation, evidenced by the presence of inflammatory biomarkers in peripheral blood and cerebrospinal fluid.[42] Molecular markers of interest include inflammasomes NLRP1, NLRP3, and NAIP-NLRC4, as well as pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor alpha, and C-peptide.[42] Furthermore, a deterioration in cerebral blood flow autoregulation has been documented, increasing neuronal tissue vulnerability to ischemic episodes.[41,42]

Particular attention has been given to CCH, defined as a sustained reduction in cerebral blood flow of up to 40%, either focal or generalized. This condition has been associated with the progression of VCD from its preclinical stages to manifestations of established dementia.[33,41] Murine models, in which unilateral or bilateral stenosis of the common carotid artery is induced, have been fundamental in understanding the relationship between chronic hypoperfusion and secondary cognitive impairment.[33]

The clinical presentation of VaD is highly heterogeneous and depends on the specific subtype and the anatomical location of the lesions.[43] It can range from subtle cognitive processing delays to severe functional loss that impairs patient independence. Although clinical evolution is often fluctuating, it is common for the impact on daily functionality to be greater than memory deficits. Additional signs and symptoms include the presence of focal neurological signs, early gait disturbances – frequently accompanied by falls – urinary incontinence, and pseudobulbar symptoms such as emotional lability, dysarthria, and dysphagia.[43]

Among the subtypes of VaD, dementia associated with large vessel damage, also known as multi-infarct dementia, is recognized. This originates from one or multiple cerebral infarcts that affect the territories supplied by large-caliber vessels. Clinical manifestations vary depending on the affected vessel.[43] For example, damage to the anterior cerebral artery may cause motor deficits, loss of initiative, and executive function alterations; if the lesion involves the prefrontal region, disinhibition, apathy, or agitation may be observed, and in cases where the dominant hemisphere is involved, transcortical motor aphasia can develop.[43] Damage to the middle cerebral artery is associated with motor or sensory aphasias, depending on the affected branch, and may be accompanied by visual or motor neglect, various apraxias – such as visoconstructive or dressing apraxia – amusia, or Gerstmann's syndrome, characterized by finger agnosia, acalculia, right-left disorientation, and agraphia, typically due to damage to the left angular gyrus. Finally, damage to the posterior cerebral artery may result in conditions such as Anton's syndrome, characterized by cortical blindness with denial of the visual deficit, or Balint's syndrome, which includes optic ataxia, altered visual fixation, and simultanagnosia.[43] In addition, damage to the splenium of the corpus callosum can result in alexia without agraphia, while hippocampal damage has been linked to specific amnesic syndromes.[43]

FTD

Dementia represents one of the main public health challenges of the 21st century. According to estimates from the WHO, by 2025, approximately 1.2 billion people will be over the age of 60, and 75% of them will reside in developing countries. It is expected that the prevalence of dementia will double every 20 years, reaching 42.3 million cases in 2020 and projected to rise to 81.1 million by 2040, highlighting the urgent and sustained need for clinical and scientific attention in this area.[7]

In this context, FTD constitutes a heterogeneous group of neurodegenerative diseases that share the common characteristic of progressive atrophy of the frontal and anterior temporal lobes.[7] Its typical clinical manifestation includes progressive changes in behavior, executive function deterioration, and, in certain variants, language impairment.[7,44] From a pathophysiological perspective, significant neuronal loss, reactive gliosis, and microvascular alterations are observed, with an initial pattern often localized in the anterior cingulate cortex.[7]

A meta-analysis published in 2013, which included 73 studies on early-onset dementia, positioned FTD as the second most prevalent cause within this category, with an incidence ranging from 3% to 26%.[44] It is currently recognized as accounting for up to 10% of early-onset dementia cases and is the most frequent cause of neurodegenerative cognitive impairment in individuals under 65 years of age.[45-47] Across all ages, it is the third most common etiology of dementia, preceded only by AD and dementia with Lewy bodies.[47]

Clinically, the most common form of FTD is the behavioral variant (bvFTD), which accounts for more than 50% of cases. It is characterized by progressive social disinhibition, loss of empathy, impulsive behaviors, and apathy.[7] Notable changes in personality, eating behavior alterations, as well as impairments in judgment and introspection, are commonly observed.[7,44,45] Unlike other dementias, temporal-spatial orientation is usually preserved in the early stages.[43,45] The average time between the onset of symptoms and medical evaluation exceeds 3 years, and a significant proportion of patients, nearly 20%, presents with early Parkinsonian symptoms. In addition, up to 40% may develop motor neuron disease, further complicating clinical management.[43,47,48]

From a diagnostic perspective, behavioral findings such as disinhibition, apathy, lack of empathy, stereotyped behaviors, eating disturbances, and executive deficits with relatively preserved memory are key in identifying the condition.[7] Structural neuroimaging using MRI shows asymmetric atrophy, predominantly frontal or temporal, with greater involvement of the right hemisphere in many cases.[7,48] Functional studies using functional MRI have shown a decrease in connectivity between the anterior cingulate cortex and the frontoinsular region, areas that are actively involved in processing emotional and social information.[45,48] The topographic classification of atrophy includes frontal-dominant, temporal, frontotemporal, and frontotemporoparietal forms. In addition, in patients with mutations in the *MAPT* gene, elevated uptake of the radiotracer flortaucipir (F-Av-1451) has been documented in frontal and temporal cortical regions, which may be useful as an *in vivo* biomarker[7,45,48] (Table 1).[7,44,45,47,48]

Another relevant clinical presentation within the FTD spectrum is primary progressive aphasia (PPA), which can be divided into two main variants. The non-fluent variant manifests as slow, halting speech with phonetic errors, accompanied by difficulties in language structure and praxis. The average age of onset is around 60 years, though it can occur between ages 40 and 80. MRI imaging shows atrophy of the dominant lower frontal lobe, insula, and supplementary motor area.[7,44,45,48] On the other hand, the semantic variant involves a progressive loss of word meaning, superficial dyslexia, difficulties identifying objects, and prosopagnosia.[7,45] It usually begins between ages 55 and 70 and is associated with atrophy of the left anterior temporal lobe, which in advanced stages may extend to visual, parietal, and occipital regions.[47,48]

From a neuropathological perspective, FTD is grouped under the term frontotemporal lobar degeneration (FTLD), a condition characterized by marked neuronal loss and gliosis.[45] According to the predominant abnormal protein, several variants have been described: FTLD-tau, FTLD-TDP, FTLD-FUS, and FTLD-UPS, with the latter being characterized by ubiquitin-only inclusions or the absence of visible inclusions.[47,48] Among the most studied proteins, pathological tau stands out due to its hyperphosphorylation, a process that alters its microtubule-stabilizing function and generates insoluble aggregates.[7] At least 85 putative phosphorylation sites have been described, and their pattern contributes to the clinical heterogeneity observed. The clinical-pathological subtypes associated with this alteration include corticobasal degeneration, progressive supranuclear palsy, and Pick's disease, representing approximately 35%, 31%, and 30% of cases, respectively.[7,48]

Table 2. Different types of dementia[46,48,50]

Types of dementia	Brain atrophy	Magnetic resonance	Computed tomography	Positron emission tomography (FDG-positron emission tomography)	SPECT (brain perfusion)	Microinfarcts or vascular lesions	Inclusion bodies (Aβ/tau "AD" and TDP-43/FUS "frontotemporal dementia")
Frontotemporal dementia	Predominantly in frontal and temporal lobes, in the gray matter	Asymmetric frontal and temporal atrophy. Dilation of the anterior ventricles	Marked frontal and temporal atrophy, possible ventricular dilation	Hypometabolism in anterior frontal and temporal lobes	Hypoperfusion in frontal and temporal lobes	Not present	Protein inclusions, depending on the type, the most common being TDP-43 or TAU
Alzheimer's disease	It initially affects the hippocampus and entorhinal cortex, then the temporal and parietal lobes	Early hippocampal atrophy, which progresses to other cortical areas	Progressive global atrophy, marked in the medial temporal lobe	Hypometabolism in hippocampus and temporal and parietal cortex	Hypoperfusion in parietotemporal regions	Not present	Amyloid beta deposition and Tau tangles
Vascular dementia	Variable, focal or diffuse, depending on the location of the infarct	Leukoaraiosis, white matter hyperintensities	Periventricular white matter hypodensities	Heterogeneous hypometabolism, depending on the affected area	Heterogeneous hypoperfusion with focal ischemic area	Multiple infarcts, white matter hyperintensities (leukoaraiosis)	Ischemic lesions, fibrin deposits, and vascular alterations

SPECT: single-photon emission computed tomography.

Regarding genetics, it is estimated that around 30% of FTD cases exhibit an autosomal dominant hereditary pattern. Genes most commonly implicated are GRN, MAPT, and C9orf72.[7,44,46,48] The *GRN* gene, located on chromosome 17, encodes progranulin, a protein involved in inflammation, tissue repair, and autophagy processes; at least 70 pathogenic mutations have been identified, which lead to haploinsufficiency.[44,46] MAPT, also on chromosome 17, encodes the tau protein and has more than 50 known mutations, associated with microtubule dysfunction and neuronal degeneration.[44,46] Meanwhile, C9orf72, located on chromosome 9, contains abnormal expansions of the G4C2 motif in its first intron. These expansions generate neurotoxicity through three main mechanisms: haploinsufficiency, RNA toxicity, and the production of toxic dipeptide proteins.[7,44,46] It is considered the most frequent genetic cause of FTD and shares pathophysiological mechanisms with amyotrophic lateral sclerosis, which coexists in a significant percentage of cases. In addition, between 10% and 15% of patients with this mutation may present psychotic symptoms, adding complexity to the clinical diagnosis.[7,46]

FTD comprises a group of disorders characterized by focal degeneration of the frontal and temporal lobes, manifesting as changes in behavior, language, or executive function.[7,44,45] Clinically, FTD includes three major variants:

- Behavioral variant (bvFTD) – progressive disinhibition, apathy, and social withdrawal
- Semantic variant PPA (svPPA) – loss of word meaning and object recognition
- Non-fluent/agrammatic variant (nfvPPA) – effortful, halting speech with grammatical errors.

Genetically, approximately 30% of FTD cases are linked to mutations in GRN, MAPT, or C9orf72 genes.[7,44,46]

The diagnosis of FTD represents a significant clinical challenge. Its heterogeneous presentation and symptomatic overlap with various psychiatric disorders can delay timely recognition and treatment.[43,44] A comprehensive evaluation combining detailed clinical history, neuropsychological tests, behavioral analysis, and neuroimaging studies is essential. Structural MRI and PET are currently the most widely used tools for identifying cortical atrophy patterns and evaluating functional connectivity.[7,48] In recent years, biomarkers have become increasingly relevant. Neurofilament light chain (NfL), measurable in both plasma and CSF, is currently the most robust progression biomarker for FTD, reflecting axonal degeneration.[7,44,49] Although tau PET has proven valuable in AD, it shows limited reliability in FTD, as most subtypes demonstrate off-target binding or absent uptake.[45,48] Consequently, FTD biomarker development remains focused on fluid markers (NfL, progranulin levels) and genetic testing, integrated with MRI-based atrophy patterns for subtype differentiation.

Differential diagnosis

The differential diagnosis of FTD requires a comprehensive and detailed clinical evaluation.[7,48] It is essential to investigate the family history of neurodegenerative diseases and analyze the progression and pattern of behavioral changes in the patient. The evaluation should be complemented with formal neuropsychological tests and neuroimaging studies (such as MRI or PET), along with direct observation of specific behavioral alterations.[7,48,50]

Laboratory studies should be conducted to rule out treatable causes of cognitive decline. These include a complete blood count, kidney and liver function tests, thyroid evaluation, and serum vitamin B12 levels, among others.[7,49]

However, it is important to note that neurodegeneration patterns observed in neuroimaging represent indirect markers of the pathological subtypes of FTD and do not always allow for a definitive clinical diagnosis.[45,48,50] For further details, the diagnosis of the types of dementia discussed in this article (Table 2).[46,48,50]

Treatment

To this day, there are no curative therapies or specific pharmacological interventions for FTD.[7,44] Treatment is based on symptomatic management, with partial efficacy. Pharmacotherapy primarily targets the modulation of neurotransmitter systems. Selective serotonin reuptake inhibitors, such as sertraline or fluoxetine, have been used to control behavioral symptoms such as impulsivity, irritability, or disinhibition.[7,44]

In cases with psychosis, aggression, or severe agitation, the use of atypical antipsychotics may be considered. However, caution is required due to the risk of adverse effects, and it is important to note that there have been no randomized controlled clinical trials formally supporting their efficacy in this population.[7,44]

In recent years, several monoclonal antibodies targeting amyloid-β have emerged as potential disease-modifying therapies for AD. These agents, aducanumab, lecanemab, and donanemab, have been approved or are under regulatory review in various countries for use

in patients with early or mild symptomatic AD who show evidence of amyloid pathology confirmed by PET or CSF biomarkers. Their mechanism of action involves promoting amyloid clearance from the brain parenchyma, thereby slowing clinical progression.[51]

Aducanumab, targeting Aβ aggregates, showed initial promise with delayed clinical decline in early trials but was ultimately discontinued due to ineffectiveness in later phase studies and complex development issues despite FDA approval in 2021. Lecanemab binds soluble Aβ protofibrils and demonstrated significant reduction in cerebral Aβ levels, leading to its FDA approval for early symptomatic AD, signifying progress in disease-modifying therapies. Donanemab, which targets modified Aβ deposits, also received FDA approval in 2024, showing efficacy in reducing amyloid plaques and associated tau burden, though its safety profile is under ongoing evaluation.[51]

For tau, several antibodies have been evaluated. Semorinemab, a humanized anti-tau antibody, exhibited high tolerability but did not significantly slow disease progression in Phase II trials. Tilavonemab targeted extracellular aggregated tau but was discontinued due to safety concerns. Other tau antibodies such as BMS-986446 and ADEL-Y01 are still under early-stage clinical trials, focusing on safety, tolerability, and preliminary efficacy.[51]

Non-pharmacological interventions

Non-pharmacological therapies play a key role in the comprehensive management of FTD.[45] Speech and language therapies, combined with non-invasive brain stimulation techniques such as transcranial direct current stimulation, have shown significant benefits in improving symptoms related to aphasia.[45]

In addition, there is evidence suggesting that in patients with familial FTD, increasing physical activity and cognitive stimulation could be associated with a slower clinical progression.[7,45]

Therefore, the therapeutic approach continues to be mostly supportive, integrating both pharmacological and non-pharmacological measures, with the goal of preserving the patient's quality of life and functionality for as long as possible.[7,45]

Box 1. Clinical management of vascular dementia (VaD) and VCD

Diagnostic frameworks:

– Use standardized criteria such as VASCOG, VICC, or National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), integrating clinical, imaging, and neuropathological evidence
– Identify markers of CSVD: leukoaraiosis, lacunar infarcts, microbleeds, and periventricular white matter hyperintensities (Fazekas score).

Core management principles:

– Aggressive control of vascular risk factors:
  • Blood pressure < 130/80 mmHg; use of ACE inhibitors or ARBs.
  • Optimal glycemic control (HbA1c < 7%).
  • Lipid management with statins.
– Antithrombotic therapy:
  • Antiplatelet agents (aspirin, clopidogrel) in patients with previous cerebrovascular events.
  • Anticoagulation if atrial fibrillation is present.
– Lifestyle and rehabilitation:
  • Regular physical exercise (≥ 150 min/week).
  • Mediterranean or DASH diet.
  • Cognitive training, occupational therapy, and management of depression.

Follow-up:

– Neuroimaging every 12-24 months to monitor progression.
– Patient and caregiver education to enhance adherence and functional autonomy.

Early and continuous management of vascular risk factors remains the most effective strategy to prevent or slow the progression of vascular cognitive impairment.

Discussion

This review highlights the clinical and etiological complexity of the main dementias: AD, vascular dementia (VaD), and FTD.[5,6] Although all share progressive cognitive decline, they differ in their pathophysiological mechanisms, risk factors, and clinical manifestations, which complicates their diagnosis and treatment.[5-7]

One of the most relevant findings is the influence of modifiable risk factors – such as educational attainment, physical inactivity, hypertension, obesity, smoking, diabetes, and pollution – on dementia development, especially in developing countries.[2,3,9,10,11,16,18] This reinforces the importance of preventive strategies from early life stages.[3]

In AD, while beta-amyloid plaques and tau tangles have been considered diagnostic cornerstones, recent studies suggest that they are not the primary cause of neuronal damage.[4,8,26] For VaD, the role of CCH and cumulative vascular damage is emphasized.[27,33,41,42] In FTD, clinical variability and overlap with psychiatric disorders make detection challenging, though advances

in neuroimaging and biomarkers are improving diagnosis.[7,44,49,50]

Given that none of these dementias has a curative treatment, current therapies focus on symptomatic management.[5,7,44] Non-pharmacological interventions such as cognitive stimulation and physical activity are particularly valuable for preserving functionality and quality of life.[12,18,45]

While this review has the inherent limitations of a narrative approach, it offers an updated and critical perspective on the main types of dementia, emphasizing the urgent need to strengthen prevention and timely diagnosis.[3,4,7,45]

Conclusion

Dementia represents a global health challenge, with its escalating prevalence underscoring the urgent need for heightened awareness and action. While curative treatments remain elusive, this review highlights the critical importance of understanding modifiable risk factors and early intervention strategies. Future guidelines must prioritize robust public health initiatives focused on prevention, timely diagnosis, and comprehensive supportive care. Continued research into the complex etiologies and novel therapeutic targets is paramount to mitigating the profound impact of dementia on individuals and societies worldwide.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence (AI). The authors declare that an artificial intelligence tool was used to support the preparation of this manuscript. Specifically, ChatGPT (OpenAI) was used as a language-support tool to improve the grammar, clarity, and readability of certain sections of the text. The AI tool was not used for literature searches, data analysis, or the interpretation of scientific findings. All content was critically reviewed and approved by the authors, who take full responsibility for the final version of the manuscript.

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REVIEW ARTICLE

Confirmatory tests in brain death determination: a critical role in posterior fossa lesions

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Abstract

The determination of brain death or death by neurological criteria (BD/DNC) typically relies on clinical assessment: coma, absence of brainstem reflexes, and apnea. However, in cases with primary posterior fossa lesions, clinical criteria alone may be insufficient. Unlike supratentorial injuries, these lesions can selectively impair brainstem function without causing global cerebral circulatory arrest or significantly increasing intracranial pressure. As a result, patients may retain cerebral blood flow (CBF) and electroencephalogram (EEG) activity despite meeting clinical BD/DNC criteria. In such cases, confirmatory tests are not discretionary but diagnostically essential. Evaluations of bioelectrical activity (e.g., EEG and evoked potentials) and CBF (e.g., transcranial Doppler, computed tomography angiography, and radionuclide imaging) provide critical confirmation, reducing diagnostic errors and supporting ethical and legal standards. Clinical cases, including the widely known case of Jahi McMath, highlight the risks of declaring brain death without confirmatory confirmation in posterior fossa injuries. Therefore, BD/DNC protocols must be updated to require confirmatory testing when posterior fossa pathology is present, when clinical findings are unclear, or when a comprehensive examination is not feasible. This clinical viewpoint, accompanied by a literature synthesis, calls for an urgent revision of protocols, enhanced clinician education, and institutional preparedness to ensure that brain death determinations remain accurate, ethical, and credible.

Keywords: *Confirmatory tests. Tests. Brain death/death by neurological criteria. Brainstem. Posterior fossa lesions.*

Pruebas confirmatorias en la determinación de la muerte encefálica: un papel crucial en las lesiones de la fosa posterior

Resumen

La muerte encefálica o muerte por criterios neurológicos (BD/DNC) se determina clínicamente mediante coma, ausencia de reflejos del tronco encefálico y prueba de apnea. No obstante, en lesiones primarias de la fosa posterior, estos criterios pueden ser insuficientes. A diferencia de las lesiones supratentoriales, las de la fosa posterior pueden comprometer selectivamente el tronco encefálico sin provocar un paro circulatorio cerebral global ni un aumento marcado de la presión intracraneal. Por ello, algunos pacientes pueden mantener flujo sanguíneo cerebral y actividad electroencefalográfica, a pesar de cumplir criterios clínicos de BD/DNC. En estos contextos, las pruebas confirmatorias no deben ser opcionales, pues son esenciales para el diagnóstico. Estudios de la actividad bioeléctrica (como EEG y potenciales evocados) y del flujo cerebral (como angiografía de los 4 vasos, Doppler transcraneal, angiotomografía, gammagrafía cerebral, angioresonancia) proporcionan evidencia crítica que refuerza la certeza diagnóstica y previene errores éticos y legales. Casos clínicos como el de

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Jahi McMath JM) demuestran los riesgos de declarar la muerte encefálica sin estas confirmaciones en lesiones de la fosa posterior. Este artículo de Perspectiva Clínica con síntesis de la literatura plantea la necesidad urgente de actualizar los protocolos de BD/DNC, exigir pruebas complementarias en estos casos, fortalecer la formación médica y asegurar que las instituciones estén preparadas para garantizar determinaciones éticas, precisas y confiables.

Palabras clave: *Pruebas confirmatorias. Muerte encefálica/muerte por criterios neurológicos (BD/DNC). Tronco encefálico. Lesiones de la fosa posterior.*

Introduction

The clinical diagnosis of brain death/death by neurological criteria (BD/DNC) has long served as a cornerstone of medical, ethical, and legal standards for declaring death. Historically, the bedside neurological examination – including the demonstration of coma, absence of brainstem reflexes, and a positive apnea test – has been considered sufficient in most cases. However, in specific clinical contexts, particularly those involving primary posterior fossa lesions, reliance solely on clinical criteria becomes precarious. In these cases, confirmatory tests should not be viewed as supplementary. Still, they are indispensable components in determining BD/DNC.[1-6]

This article is presented as a clinical viewpoint, synthesizing the current literature. Posterior fossa lesions, such as basilar artery thrombosis, brainstem hemorrhages, or cerebellar infarctions, can profoundly impair brainstem function while paradoxically preserving supratentorial structures, cerebral blood flow (CBF), and electroencephalographic (EEG) activity.

Dr. Machado's seminal work elucidated that posterior fossa lesions may not elevate intracranial pressure (ICP) as significantly as supratentorial lesions do, as seen in the Jahi McMath case. In supratentorial injuries, progressive edema leads to a critical rise in ICP, reducing cerebral perfusion pressure and culminating in a complete cessation of CBF. In contrast, posterior fossa lesions, due to the confined anatomical compartment, often lead to selective brainstem dysfunction without necessarily causing a full rise in ICP or global circulatory arrest. This anatomical and pathophysiological distinction explains why patients with posterior fossa damage may retain residual cortical functions despite meeting clinical criteria for brain death.[7-13] The persistence of EEG activity and CBF in posterior fossa injuries challenges the traditional assumptions underlying BD/DNC protocols.

The preservation of supratentorial electrical and circulatory function, despite brainstem failure, underscores the necessity for confirmatory testing to avoid erroneous and premature declarations of death. Without confirmatory confirmation, there exists a significant risk of diagnosing brain death in patients who retain some cerebral functions.[2,7,14-23] Confirmatory tests, which include evaluations of bioelectrical activity (EEG, somatosensory, and brainstem auditory evoked potentials) and assessments of cerebral perfusion (transcranial Doppler [TCD], cerebral angiography, radionuclide imaging, and computed tomography [CT] perfusion), offer critical diagnostic insights that the clinical examination alone may miss. Their bedside applicability further enhances their practicality in intensive care settings, ensuring that diagnostic certainty can be achieved without unnecessary delays.[24-28] It is, however, crucial to acknowledge that these tests have limitations, including technical variability, interpreter dependence, and potential confounders such as hypothermia or sedative drugs.

Diagnostic rationale and supporting evidence

The value of confirmatory tests in posterior fossa lesions is multifaceted. Magnetic resonance imaging (MRI) plays a pivotal role in the initial diagnostic workup by precisely delineating the structural etiology of the posterior fossa lesion (e.g., infarct, hemorrhage, tumor, and demyelination), which is crucial for understanding the pathophysiology and anticipating potential diagnostic challenges in the BD/DNC determination process. This is particularly critical because CT, while often the first-line imaging modality in emergencies, has limited sensitivity and specificity in the posterior fossa due to beam-hardening artifacts from the surrounding bone. MRI, with its superior soft tissue resolution and multi-planar capabilities, provides an unparalleled view of brainstem anatomy and pathology, allowing for a definitive diagnosis of the lesion's nature and extent. This precise anatomical information is the essential foundation upon which the subsequent need for and interpretation of confirmatory tests for BD/DNC is built.[16-19]

Detection of residual function

EEG and multimodality evoked potentials can detect preserved cortical and subcortical activity that clinical examination might overlook. Somatosensory evoked potential, particularly the presence of cortical N20 responses, provides evidence of residual thalamocortical function.[29-32] However, the sensitivity of EEG can be reduced by factors such as hypothermia (< 36 °C), metabolic disturbances, or high doses of barbiturates, potentially leading to false-negative results (i.e., electrocerebral silence despite preserved neuronal function). A significant concern is the potential for false-negative results, particularly with electrophysiological studies such as EEG. For instance, severe hypothermia (typically below 32 °C), metabolic disturbances, or the presence of central nervous system depressant drugs (e.g., barbiturates, benzodiazepines, and anesthetic agents) can induce or mimic electrocerebral silence, creating the appearance of a complete lack of brain activity even in a patient who is not brain dead. This underscores the non-negotiable prerequisite of first excluding and correcting for these major confounders before performing and interpreting ancillary tests. The diagnostic approach must also be adjusted for special populations. In pediatric patients, the nervous system is still developing, and guidelines often mandate more extended observation periods and a higher inclination toward confirmatory testing. In post-operative patients, particularly after posterior fossa surgery, clinical findings can be obscured by edema, sedation, or surgical manipulation, making confirmatory tests indispensable.[11,12]

While ancillary tests are essential for diagnostic certainty, their limitations must be acknowledged to avoid misinterpretation. A diagnosis of BD/DNC cannot be established solely on an ancillary test result if these conditions are present and uncorrected; the clinical examination and the ancillary test must both be performed under optimal conditions to be valid.

Confirmation of cessation of circulation

Imaging studies revealing absent cerebral circulation provide robust evidence of irreversible brain failure. Techniques such as TCD, CT angiography, and radionuclide imaging are crucial to identify complete circulatory arrest.[24,33-36] The sensitivity and specificity of these flow studies are high but not absolute. For instance, TCD sensitivity for confirming circulatory arrest is estimated at 90-95%, specifically at 98-100%, but it can be technically challenging in patients with poor acoustic windows. CT angiography has a sensitivity and specificity of nearly 95-100% but requires strict adherence to protocol regarding timing and contrast injection.

Ethical safeguard

Utilizing confirmatory tests in these high-risk contexts respects patient dignity, prevents false positives, and sustains public trust in medical determinations of death.[11] Clinical evidence robustly supports these assertions. Reports by Ferbert, Varela, and Esteban demonstrate preserved EEG or CBF in patients with devastating posterior fossa injuries who met clinical BD criteria based solely on bedside examination.[37-40]

A literature review reveals documented pitfalls. For example, Wagner et al. reported a case of apneic coma with absent brainstem reflexes but preserved cortical somatosensory evoked potential, highlighting the potential for misdiagnosis without confirmation.[14] Varelas et al. documented a case series where 15% of patients with primary posterior fossa lesions meeting clinical BD/DNC criteria had preserved supratentorial blood flow on angiography.

The imperative for ancillary testing must be balanced with the stark reality of global healthcare disparities. The availability of advanced neuroimaging (CT angiography and MRI), nuclear medicine, and even continuous EEG is often limited in low-resource settings. This scarcity poses a significant ethical and practical challenge, potentially creating a dangerous diagnostic gap where the patients most vulnerable to misdiagnosis – those with posterior fossa lesions – are also those with the least access to confirmatory technology. To address this, protocols in these regions must emphasize a more rigorous and prolonged clinical observation period, leveraging any available ancillary tools, such as careful serial neurological examinations and, if equipment and expertise are available, TCD. Furthermore, this disparity underscores an urgent call to action for the global medical community: to support the development and dissemination of cost-effective, portable technologies (e.g., simplified EEG devices and contrast-enhanced ultrasound techniques) and to foster telemedicine collaborations that can provide remote expert interpretation, thereby bridging the gap in diagnostic accuracy and ensuring equitable standards for determining death worldwide.[11]

The Jahi McMath's case highlighted that preserved EEG activity and cerebral anatomy persisted months

Table 1. Contrasting supratentorial and posterior fossa lesions in BD/DNC determination

Feature	Supratentorial lesions	Posterior fossa lesions
Primary mechanism	Mass effect, raised ICP, herniation	Direct brainstem destruction/compression
ICP elevation	Typically severe and global	Often minimal or localized
Cerebral blood flow	Globally absent in BD/DNC	May be preserved supratentorially
EEG activity	Electrocerebral silence	May remain present
Confirmatory test role	Confirmatory	Often essential for diagnosis
Main diagnostic risk	False positive (rare with strict criteria)	False positive (declaring BD/DNC with preserved cortical function)

BD/DNC: brain death or death by neurological criteria; ICP: intracranial pressure; EEG: electroencephalogram.

after her initial BD/DNC declaration, emphasizing the critical need for confirmatory tests in similar scenarios. Jahi's case serves as a stark reminder that, without confirmatory tests, misdiagnoses can have profound ethical, legal, and societal consequences.[41-46] The pathophysiology of posterior fossa injuries uniquely enables the preservation of supratentorial function. Unlike massive hemispheric injuries that rapidly increase ICP and extinguish global cerebral perfusion, posterior fossa lesions may selectively damage brainstem structures without inducing total intracranial circulatory arrest. Moreover, these lesions may compromise vital autonomic centers, leading to cardiorespiratory instability without necessarily abolishing cortical activity, further complicating the clinical picture.[2,7,47,48]

In table 1, a comparison of BD/DNC in supratentorial versus infratentorial lesions is presented.

Proposed diagnostic algorithm and legal considerations

Recommendations are clear and urgent: BD/DNC protocols must require confirmatory tests in cases involving primary posterior fossa lesions. Incomplete, ambiguous, or equivocal clinical findings. Barriers to performing a comprehensive neurological examination due to trauma or anatomical constraints. Clinical suspicion of preserved supratentorial function despite apparent brainstem failure. Cases involving severe metabolic, toxicological, or pharmacological confounders that could mimic brain death.

Based on the synthesized evidence, we propose the following diagnostic algorithm for BD/DNC determination when posterior fossa pathology is suspected or present.

Prerequisites

Establish the irreversible and proximate cause of coma, and exclude major confounders (hypothermia, hypotension, severe metabolic/acid-base disturbances, drug intoxication, and neuromuscular blockade).

Complete clinical examination

Perform a full clinical BD/DNC examination (coma, absent brainstem reflexes, and positive apnea test).

Decision point: posterior fossa lesion or uncertain examination?

- No: BD/DNC can be declared on clinical grounds alone (per institutional protocol).
- Yes: proceed to Step 4.

Testing mandatory

Perform a confirmatory test. Choice depends on availability, expertise, and patient factors:

Blood flow study options include

CT angiography, four-vessel angiography, radionuclide scintigraphy, or TCD, MRI angiography,

Bioelectrical activity study

EEG or multimodal evoked potentials (SSEPs).

Interpretation

BD/DNC is confirmed only after the confirmatory test demonstrates either cessation of intracranial blood flow (e.g., absent opacification on CTA and no intracranial uptake on scintigraphy) or loss of bioelectrical activity (electrocerebral silence on EEG and absent cortical responses on SSEP).

Documentation and declaration: document all steps and findings

Declare BD/DNC. The legal landscape for BD/DNC determination varies significantly across jurisdictions. In the United States, the revised Uniform Determination of Death Act (UDDA) leaves "*accepted medical standards*" to professional guidelines, which are evolving toward mandating confirmatory tests in complex cases.[3,4] In many Latin American and European countries, national laws often explicitly require confirmatory testing in all BD/DNC determinations, as is the case in Cuba.[11]

This variability necessitates clinicians to be intimately familiar with the specific legal statutes and medical guidelines governing BD/DNC in their own country and institution**.** Institutions and professional societies must update their policies to reflect these complexities. In addition, critical care, neurology, and neurosurgery training programs must emphasize the importance of confirmatory testing in complex BD/DNC cases. Policymakers should ensure that every hospital authorized to determine brain death has the necessary tools and expertise to perform and interpret confirmatory studies.[3,4,6,49] This is particularly challenging in low-resource settings, where access to advanced imaging or neurophysiology may be limited, underscoring the need for regional adaptations and potential telemedicine solutions.[7]

The evolution of BD/DNC criteria must keep pace with the advancement of knowledge. Considering mounting evidence and documented cases such as Jahi McMath, continuing to declare brain death without mandatory confirmatory confirmation in posterior fossa injuries poses increasing ethical and clinical risk and warrants urgent reconsideration. A failure to adapt risks not only individual injustice but systemic erosion of trust in medical and legal determinations of death.[41-43,45]

The legal weight of a BD/DNC determination necessitates an understanding of its jurisdictional variations, which directly impact the role of ancillary testing. The legal framework is highly heterogeneous: while the United States' revised UDDA defers to "accepted medical standards," allowing professional society guidelines to dictate the use of ancillary tests (often making them mandatory in complex cases like ours), 11 many countries have more prescriptive laws. In numerous Latin American nations (e.g., Mexico and Argentina) and across much of Europe, national statutes frequently explicitly require at least one ancillary test to confirm all brain death diagnoses, regardless of clinical scenario. This legal imperative removes clinical discretion and makes ancillary testing a mandatory step for a death declaration. Conversely, other jurisdictions may not legally recognize ancillary tests at all, creating a potential conflict between best medical practice and legal doctrine. This variability underscores the critical importance of clinicians being intimately familiar with the specific statutes and medical guidelines governing BD/DNC in their own country and institution to ensure determinations are both medically sound and legally defensible.[27,28,40]

In conclusion, confirmatory testing in the diagnosis of brain death is critical when dealing with posterior fossa lesions. Such integration will uphold the truthfulness of death determinations, reinforce ethical medical practice, and maintain the public's trust in end-of-life decision-making. Medicine must remain vigilant, responsive to emerging evidence, and unwavering in its commitment to accuracy and dignity at the most critical moments of human life.[7,11]

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Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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