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EDITORIAL

Beyond diagnosis: integrating mechanisms, function, and patient-centered care in neurology

Más allá del diagnóstico: integrando mecanismos, función y atención centrada en el paciente en neurología

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Neurology has traditionally been built around the ability to recognize syndromes, localize lesions, and establish an etiological diagnosis. These skills remain at the core of neurological practice. However, contemporary neurology increasingly requires us to move beyond diagnosis itself. Understanding disease mechanisms, identifying meaningful biomarkers, anticipating functional consequences, and recognizing the individual experience of neurological disease have become equally important components of care.

The articles included in this issue of *Revista Mexicana de Neurociencia* illustrate this transition from disease identification to a broader and more integrated view of neurological disorders. Although they address apparently distinct areas – from learning and memory to genetic disease, neuromuscular disorders, cerebrovascular complications, intracranial pressure, and Parkinson's disease – they share a common message: diagnosis is an essential starting point, but it is rarely the final objective of neurological care.

One example is post-stroke dysphagia. Stroke outcome is frequently assessed through neurological deficit and global disability, yet complications such as dysphagia may substantially influence recovery, nutrition, aspiration risk, pneumonia, length of hospitalization, and ultimately prognosis. The review by Solís-Gómez et al. emphasizes the wide variation in the reported prevalence of post-stroke dysphagia. It examines its risk factors, diagnostic methods, complications, rehabilitation strategies, and nutritional management. This is particularly relevant because swallowing dysfunction can be underrecognized, despite its potentially serious consequences. Its management therefore illustrates an important principle of modern stroke care: successful treatment does not end with reperfusion or stabilization of the neurological deficit. Attention must also be directed toward the complications that determine recovery and functional independence.

A different expression of the same principle can be found in rare genetic neurological diseases. Cuevas-García et al. describe an infant with riboflavin transporter deficiency associated with a homozygous nonsense variant in *SLC52A3*. The patient developed progressive neuromuscular involvement, including hypotonia, dysphagia, and respiratory failure, and showed no significant clinical improvement despite early high-dose riboflavin supplementation. The authors highlight an important genotype-phenotype relationship: severe loss-of-function variants may be associated with poorer therapeutic responses than missense variants. Here, molecular diagnosis provides more than a disease label. It may help explain phenotypic severity, inform prognosis, influence expectations regarding therapeutic response, and improve genetic counseling. Precision neurology, therefore, involves not only identifying a pathogenic variant but understanding what that variant means for an individual patient.

The increasing sophistication of diagnostic tools is also reflected in the study of myasthenia gravis.

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Galarza-Chávez et al. evaluate concordance between low-frequency repetitive nerve stimulation and anti-acetylcholine receptor antibodies. Among 106 records, the authors found high agreement when both tests were positive in patients with confirmed myasthenia gravis. At the same time, agreement was more modest when both tests were negative and the diagnosis was excluded. The study reminds us that neurological diagnosis increasingly depends on integrating clinical examination with complementary methods rather than on isolated test results. Neurophysiology and serological biomarkers should not compete with clinical reasoning; their greatest value emerges when they are interpreted within it.

Idiopathic intracranial hypertension provides another example of this integrative approach. Its clinical importance extends beyond documenting elevated intracranial pressure. Persistent headache, visual dysfunction, papilledema, and neuropsychiatric manifestations can substantially affect quality of life, while delayed recognition may result in irreversible visual impairment. The review in this issue discusses the growing role of neuroimaging, optical coherence tomography, and transorbital ultrasonography in diagnosis and monitoring, while emphasizing that treatment should be individualized and may range from lifestyle interventions and pharmacological therapy to surgical procedures in refractory disease. Importantly, substantial gaps remain regarding risk stratification, therapeutic targets, and standardized long-term follow-up. This uncertainty is itself relevant: technological advances do not eliminate the need for longitudinal clinical judgment.

Moving further from conventional disease-centered models, the review of latent inhibition by Vera-Rivera et al. reminds us that neuroscience also provides the conceptual framework through which clinical phenomena can ultimately be understood. Latent inhibition – the reduction in associative learning after previous exposure to a stimulus without apparent consequences – offers a model for studying attention, memory retrieval, learning updating, and brain plasticity. The authors trace its evolution from experimental psychology to neurobiological and translational models, including its relationship with psychopathology and salience processing. Such work represents an essential bridge between basic and clinical neuroscience. Understanding how the brain assigns relevance to stimuli, modifies associations, and updates previous learning may eventually contribute to explaining behavioral abnormalities that cannot be understood through structural abnormalities alone.

Perhaps the clearest demonstration of why neurology must move beyond conventional clinical outcomes comes from the longitudinal study of self-perceived stigma in Parkinson's disease. Guerra-Anzaldo et al. followed 117 people with Parkinson's disease for approximately 1 year. Despite significant improvements in motor symptoms, mobility, and activities of daily living, self-perceived stigma remained largely unchanged, with improvement occurring in only 29.1% of participants. Changes in perceived social support and anxiety were associated with improvement in stigma.

This finding deserves particular attention. Improvement in neurological symptoms does not necessarily translate into improvement in the patient's experience of illness. Motor scales, imaging studies, biomarkers, and functional measures provide indispensable information, but they may fail to capture social isolation, anxiety, stigma, loss of identity, or changes in interpersonal relationships. In Parkinson's disease, as in many chronic neurological disorders, these dimensions can persist even when conventional clinical outcomes improve. The authors consequently support incorporating targeted psychosocial interventions, mental health services, and stronger social support into multidisciplinary care.

Taken together, the contributions in this issue illustrate the expanding scope of neurological practice. Molecular genetics can refine prognosis; neurophysiology can strengthen diagnostic reasoning; advanced imaging and physiological measurements can improve monitoring; rehabilitation can modify functional outcomes; experimental neuroscience can reveal mechanisms of learning and behavior; and patient-reported outcomes can expose dimensions of disease that conventional neurological examination may overlook.

This expansion should not be interpreted as a departure from classical neurology. On the contrary, it represents its natural evolution. Careful clinical observation remains indispensable, but it is now complemented by molecular, physiological, imaging, cognitive, functional, and psychosocial information. The challenge is not simply to accumulate more data but to integrate them into decisions that are meaningful for patients.

Ultimately, the goal of neurological care is not merely to name a disease or quantify its severity. It is to understand how disease affects the brain, how those changes affect function, and how both influence the life of the person experiencing them. Moving beyond diagnosis, therefore, means moving toward a more complete form of neurology – one in which mechanisms inform treatment, treatment seeks meaningful functional recovery, and clinical success is measured not only by what improves on examination but also by what improves in the patient's life.

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ORIGINAL ARTICLE

Riboflavin transporter deficiency associated with a homozygous nonsense *slc52a3* variant: first genotype-phenotype correlation and literature review

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Abstract

Objective: *The objective of the study was to describe a rare case of riboflavin (RF) transporter deficiency (RTD) caused by a homozygous nonsense variant in SLC52A3 not previously associated with a detailed clinical phenotype, and to review the clinical features, genetic findings, and therapeutic response reported in the literature.* **Methods:** *We report the clinical, neurophysiological, and genetic findings of an infant diagnosed with RTD. Molecular analysis was performed using next-generation sequencing, with variant confirmation by Sanger sequencing. Variant interpretation followed the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines. In addition, a narrative review of the literature was conducted, focusing on previously reported cases of SLC52A2 and SLC52A3 mutations.* **Results:** *The patient presented with progressive neuromuscular involvement, including hypotonia, dysphagia, and respiratory failure requiring ventilatory support. Genetic testing identified a homozygous nonsense variant in SLC52A3, predicted to result in loss of protein function. This variant has been previously deposited in ClinVar by the testing laboratory but has not been reported in published clinical cases to date. Despite early initiation of high-dose RF supplementation, no significant clinical improvement was observed. Review of the literature suggests that missense variants are more frequently associated with partial therapeutic response, whereas severe loss-of-function variants, such as nonsense mutations, are associated with poorer outcomes.* **Conclusions:** *RTD should be considered in infants with progressive neuromuscular symptoms and respiratory compromise. Although early RF supplementation remains essential, this case highlights that therapeutic response may be limited in patients harboring severe loss-of-function variants, underscoring the importance of genotype-phenotype correlations for prognosis and clinical counseling.*

Keywords: *Brown-Vialetto-Van Laere syndrome. SLC52A3. Polyneuropathies. Exome sequencing. Nonsense codon.*

Deficiencia del transportador de riboflavina asociada con una variante homocigota sin sentido en SLC52A3: primera correlación genotipo-fenotipo y revisión de la literatura

Resumen

Objetivo: *Describir un caso raro de deficiencia del transportador de riboflavina causado por una variante nonsense homocigota en SLC52A3 no asociada previamente con un fenotipo clínico detallado, y revisar las características clínicas, los hallazgos*

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genéticos y la respuesta terapéutica reportada en la literatura. **Métodos:** *Reportamos los hallazgos clínicos, neurofisiológicos y genéticos de un lactante diagnosticado con deficiencia del transportador de riboflavina. El análisis molecular se realizó utilizando secuenciación de nueva generación, con confirmación de variante por secuenciación Sanger. La interpretación de variantes siguió las pautas ACMG/AMP. Además, se realizó una revisión narrativa de la literatura enfocada en casos previamente reportados de mutaciones SLC52A2 y SLC52A3.* **Resultados:** *El paciente presentó compromiso neuromuscular progresivo, incluyendo hipotonía, disfagia e insuficiencia respiratoria que requirió soporte ventilatorio. Las pruebas genéticas identificaron una variante nonsense homocigótica en SLC52A3, que se predice que resultará en pérdida de la función de la proteína. Esta variante fue depositada previamente en ClinVar por el laboratorio del análisis, pero hasta la fecha no se ha reportado en casos clínicos publicados. A pesar del inicio temprano de la suplementación con dosis altas de riboflavina, no se observó una mejoría clínica significativa. La revisión de la literatura sugiere que las variantes missense se asocian con mayor frecuencia a una respuesta terapéutica parcial, mientras que las variantes con pérdida de función grave, como las mutaciones nonsense, se asocian a peores resultados.* **Conclusiones:** *La deficiencia del transportador de riboflavina debe considerarse en lactantes con síntomas neuromusculares progresivos y compromiso respiratorio. Si bien la suplementación temprana con riboflavina sigue siendo esencial, este caso destaca que la respuesta terapéutica puede ser limitada en pacientes con variantes con pérdida de función grave, lo que subraya la importancia de las correlaciones genotipo-fenotipo para el pronóstico y el asesoramiento clínico.*

Palabras clave: *Síndrome de Brown-Vialetto-Van Laere. SLC52A3. Polineuropatías. Secuenciación de exoma. Codón sin sentido.*

Introduction

Riboflavin (RF) transporter deficiency (RTD) is a neurodegenerative genetic disorder that can progress to severe, characterized by progressive onset of motor and sensory neuropathy, caused by inactivating mutations in genes encoding RF transporters. RF, also known as vitamin B2, is a water-soluble vitamin that serves as a precursor for flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD),[1] important flavoenzymes involved in multiple metabolic pathways, mainly found in the electron transport chain (ETC) and β-oxidation of fatty acids.[2]

Intestinal absorption and uptake of RF by different organs are mediated by three RF transporters, specifically RFVT1 (encoded by the *SLC52A1* gene), RFVT2 (SLC52A2), and RFVT3 (SLC52A3).[3]

RF is absorbed in the gastrointestinal tract mainly by RFVT3[1] (Fig. 1). Within gastrointestinal cells, RF can be metabolized to FMN by RF kinase or to FAD by FAD synthetase, or it can be transported to the bloodstream by RFVT1 and RFVT2. The latter is expressed throughout the body, mostly in the brain,[4] endocrine organs, and muscle. Here, we report a pediatric case of RTD caused by a homozygous nonsense variant in *SLC52A3*, accompanied by a focused review of the literature. This report aims to expand the current genotypic spectrum of the disease and to highlight the clinical implications of severe loss-of-function variants in early-onset presentations.

Methods

A focused narrative review of the literature was conducted to contextualize RTD and its genetic basis. A bibliographic search was performed in PubMed, Google Scholar, and LILACS using a combination of MeSH terms and free-text keywords, including “Brown-Vialetto-Van Laere syndrome,” “riboflavin transporter deficiency,” “polyneuropathy,” and “nonsense mutation.” Articles published from 2012 onward reporting pathogenic variants in *SLC52A2* or *SLC52A3*, and available as full-text publications in English or Spanish, were considered eligible. Studies published before 2012, articles without reported *SLC52A2* or *SLC52A3* variants, and incomplete publications were excluded. A total of 22 articles met the inclusion criteria and were included in the narrative synthesis.

Genomic DNA extracted from a buccal swab was analyzed by whole-exome sequencing using a PCR-free library preparation workflow performed in a certified clinical laboratory. Analysis was restricted to protein-coding exons and ± 20 base pairs of flanking intronic regions. Sequencing achieved an average depth > × 35 across the reportable exome, with approximately 99.5% of targeted regions covered at ≥ × 20, ensuring high-confidence variant detection. Reads were aligned to the GRCh37/hg19 human reference genome using a validated clinical bioinformatics pipeline, and variant calling focused on a single clinically relevant transcript per gene.

A homozygous nonsense variant in *SLC52A3* was identified, introducing a premature termination codon and predicted to result in loss of protein function. Copy number variation analysis was performed, and the variant was confirmed by Sanger sequencing using an orthogonal validated method. Variant classification was performed according to the American College of

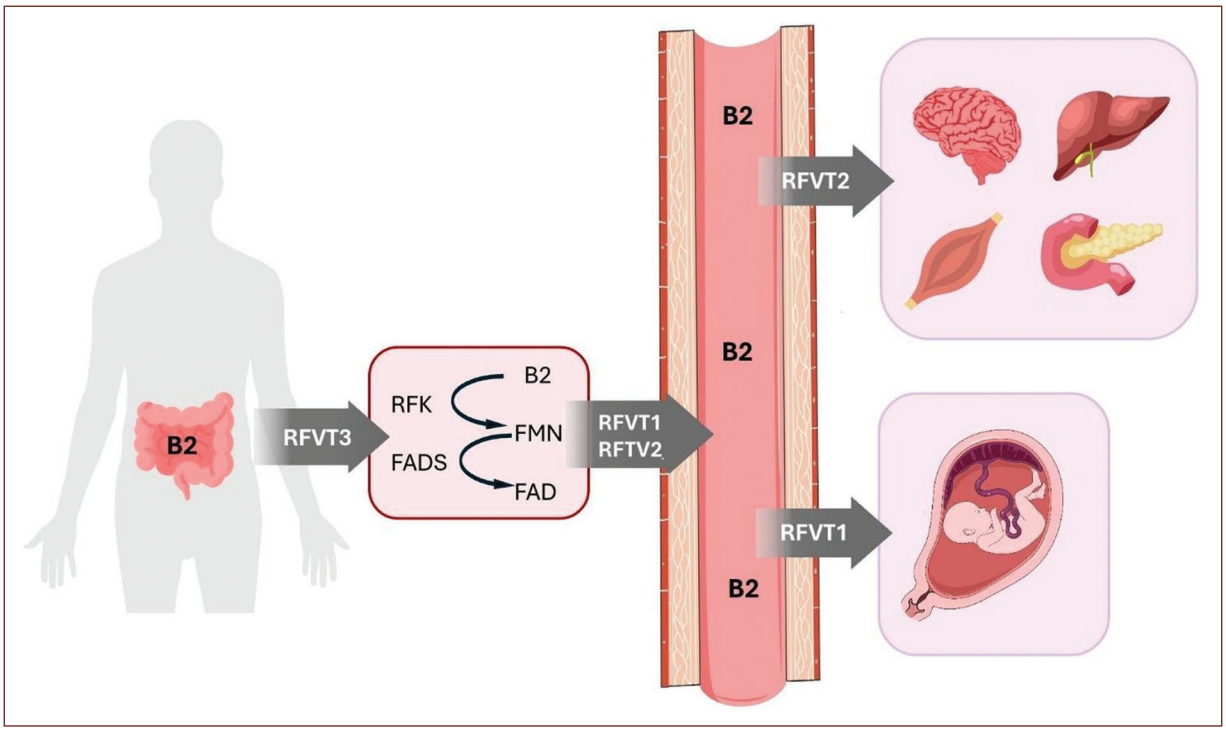

Figure 1. Distribution of riboflavin transporters. RFTV3 is abundantly expressed in the small intestine and mediates the initial absorption of riboflavin, which can be converted into riboflavin monophosphate (FMN) by riboflavin kinase. FMN may subsequently be transformed into flavin adenine dinucleotide (FAD) via FAD synthetase (FADS) or enter the circulation bound to albumin or immunoglobulins. RFTV2 is primarily expressed in the brain, liver, striated muscle, and endocrine organs, whereas RFTV1 is mainly expressed in the placenta.

Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) guidelines. Pathogenicity assessment incorporated variant type consistent with loss of function in a gene known to cause autosomal recessive disease, absence or extreme rarity in population databases, and *in silico* prediction analyses.

Functional impact prediction was evaluated using Mutation Taster, which classified the variant as disease-causing. Based on the combined evidence, the variant was classified as pathogenic.

Case report

A 12-month-old male infant, born from a full-term pregnancy by vaginal delivery, with no reported perinatal complications, no known parental consanguinity, and no significant family history of neurological or neuromuscular disease, presented with a subacute progressive neurological syndrome. Before symptom onset, the patient had normal growth parameters and age-appropriate neurodevelopment.

The clinical picture began approximately 1 month before hospital admission with an upper respiratory tract infection. Two weeks later, the patient developed an altered level of consciousness characterized by episodes of irritability alternating with drowsiness. This was followed by progressive loss of motor milestones, including difficulty maintaining head control, sitting, and standing, as well as dysphagia and intention tremor. The condition continued to deteriorate with the onset of respiratory distress, weak crying, and anorexia, which prompted hospitalization.

On admission, the patient exhibited signs of severe respiratory distress requiring mechanical ventilatory support. He was irritable and clinically dehydrated. Head circumference was between –1 standard deviation for age. Neurological examination revealed poor facial expression, incomplete gag reflex, and weak cough reflex, consistent with bulbar involvement. Muscle tone was globally decreased with preserved muscle bulk. Muscle strength was reduced with symmetric distal predominance. Deep tendon reflexes were initially

brisk and subsequently became absent as the disease progressed.

Given the rapidly progressive neuromuscular and bulbar involvement, an extensive diagnostic workup was undertaken. Brain magnetic resonance imaging (MRI) showed no structural abnormalities. Cerebrospinal fluid analysis revealed normal cytochemical and cytological findings. In view of the suspected differential diagnoses, including immune-mediated neuropathies and disorders of the neuromuscular junction, anti-ganglioside GM1 antibodies and anti-acetylcholine receptor antibodies were tested and returned negative.

Electromyography demonstrated a motor axonal neuropathy. The patient received intravenous human immunoglobulin and methylprednisolone without clinical response. Despite intensive supportive care, his condition progressed to flaccid quadriparesis, generalized areflexia, complete absence of facial expression, loss of swallowing, and permanent dependence on mechanical ventilation. Due to the severity, progression, and lack of response to immunomodulatory therapy, a genetic etiology was suspected.

Initial genetic testing included sequence analysis and deletion/duplication testing using two multigene panels: the Invitae Comprehensive Neuromuscular Disorders Panel (468 genes, including preliminary-evidence genes) and the Invitae Neurodevelopmental Disorders Panel (230 genes). Both analyses yielded non-diagnostic results. Subsequently, whole-exome sequencing was performed 5 months after symptom onset, identifying a homozygous pathogenic nonsense variant in the *SLC52A3* gene (NM_033409.3, exon 2), c.51G>A (p.Trp17*).

The identified SLC52A3 variant introduces a premature termination codon early in the coding sequence and is predicted to result in loss of function, either through severe protein truncation or nonsense-mediated mRNA decay. The variant was absent from population frequency databases, including gnomAD, and was classified as pathogenic according to ACMG guidelines.

The identified *SLC52A3* variant has only been previously deposited in the ClinVar database by the clinical laboratory that performed the exome sequencing (Invitae). However, to date, no published clinical case with detailed phenotypic characterization associated with this variant has been reported in the literature.

Based on the clinical presentation, neurophysiological findings, and molecular results, a diagnosis of RTD was established. High-dose RF therapy was initiated intravenously (iv) 10 mg/kg.d, but no clinical improvement was observed. The patient died 2 weeks later due to respiratory complications while receiving mechanical ventilatory support.

Definition

RTD, also known as Brown-Vialetto-Van Laere syndrome, is a disease with an autosomal recessive inheritance that has a prevalence of < 1/1,000,000 live births. It is due to mutations in the genes encoding RF transporters, SLC52A2 at locus 8q24 and SLC52A3 at locus 20p13,[5,6] although they have been reported in other locations.[7] It affects both sexes equally, and the age of presentation varies between 2 and 30 years. It has been described that patients with mutations in RFVT2 present manifestations at an earlier age than those who have it in RFVT3.[8]

About the disease

RTD presents clinical manifestations through two main pathways: Fatty Acid β-oxidation Chain: in RTD, decreased FAD levels resulting from transporter dysfunction impede the initial step of the fatty acid β-oxidation cycle, specifically the oxidation step. This initial step is catalyzed by acyl-CoA dehydrogenase, an enzyme that uses FAD as a cofactor to accept two hydrogen atoms, producing FADH2 and converting acyl-CoA to 2,3-enoyl-CoA. During this process, electrons flow continuously from fatty acids to the ETC via electron transfer flavoprotein (ETF)[9]. Acyl-CoA dehydrogenase donates these electrons to ETF, which then transfers them to the ETC through ETF-ubiquinone oxidoreductase (ETF-QO), ultimately reducing coenzyme Q10 (CoQ10).[10] When this process is disrupted, essential pathways like the ETC, fatty acid β-oxidation spiral, and the Krebs cycle remain incomplete, further decreasing energy production (Fig. 2).

ETC

The importance of RF deficiency lies in its crucial role for the proper function of the mitochondrial ETC. In this process, complex I and complex II participate, harboring FMN and FAD. Additionally, the mitochondrial glycerol-3-phosphate dehydrogenase enzyme, sulfide: quinone oxidoreductase, ETF, and ETF-QO are all important flavoenzymes in carrying out the process[9] (Fig. 2).

These pathways are involved in disease pathogenesis through multiple damage mechanisms, such as: Accumulation of reactive oxygen species (ROS): oxidative stress serves as an early and critical trigger of

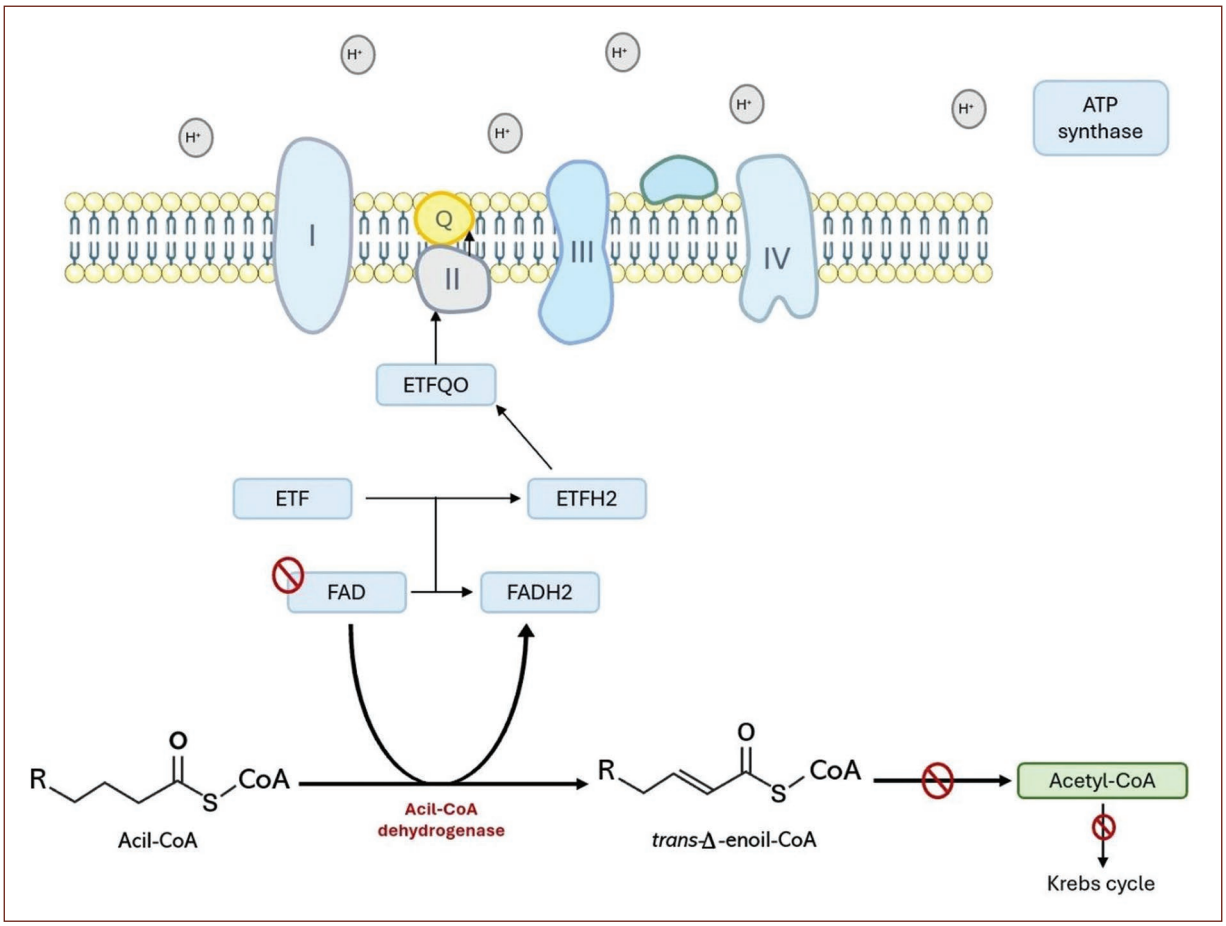

Figure 2. Pathogenic mechanisms of riboflavin transporter deficiency. Flavin adenine dinucleotide deficiency impairs electron transfer to mitochondrial complex II and the ubiquinone pool, disrupting the electron transport chain and reducing adenosine triphosphate production. In parallel, defective β-oxidation limits acetyl-CoA generation, preventing efficient Krebs cycle activity and further contributing to cellular energy failure.

cellular damage in RTD.[5] Antioxidant activity is essential for regulating ROS levels and preventing oxidative damage. Glutathione (GSH) reductase, a flavin-dependent enzyme, catalyzes the reduction of GSH disulfide to GSH, a key antioxidant peptide in cellular defense.[11] In RTD, GSH levels have a low expression compared to common cells,[12] which leads to cell degeneration with pathological consequences due to ROS accumulation.[8] It is noteworthy that protective antioxidant levels in the nervous system are lower than in other tissues, making neurons vulnerable cells.[13]

Adenosine triphosphate (ATP) depletion

Mitochondria and peroxisomes are affected in their integrity and bioenergetics in RTD syndrome.[12] Flavoproteins (proteins containing FAD or FMN as a cofactor) essential for ATP production include mitochondrial Acyl-CoA dehydrogenases and peroxisomal Acyl-CoA oxidases (ACOX), crucial in lipid catabolism. An analysis by Colasuonno et al.[12] shows a negative regulation of ACOX1 in cells from patients with RTD. ACOX1, the rate-limiting enzyme in peroxisomal β-oxidation, sees its activity reduced, decreasing efficiency in the metabolism of long-chain fatty acids. This particularly affects striated muscle cells and motor neurons, which require a lot of energy. In addition, insufficient levels of RF alter its cellular distribution and the activity of flavin-dependent enzymes, prioritizing ETC for ATP synthesis and reducing fatty acid β-oxidation.[12]

Clinical presentation

This syndrome varies in intensity, often presenting mildly before 2 years of age and progressively worsening. It is characterized by sensorineural hearing loss[6] as well

Table 1. Clinical and genetic characteristics of patients with riboflavin transporter deficiency due to *SLC52A3* variants

Case	Current case	Martínez-Esteban et al.[18]	Carreau et al.[20]	Alasqah et al.[21]	Kentab et al.[22]	Imannezhad et al.[23]
Sex	Male	Male	Female	Male	Male	Female
Age of onset	12 months	1 year and 10 months	18 years	18 months	16 months	5 years
Affected gene	SLC52A3	SLC52A3	SLC52A3	SLC52A3	SLC52A3	SLC52A3
Mutation	c. 51G > A (p.Trp17*)	c. 1156T > C (p.Cys386Arg)	c. 113G > C (p.Trp38Ser)	Not reported	c. 211G > A (p.Glu71Lys)	c. 1036C > T (p.Pro346Ser)
Variant type	Nonsense	Missense	Missense	Not reported	Missense	Missense
Consanguinity	No	Not reported	No	Yes	Yes	Yes
Initial symptoms	Hypotonia, dysphagia, weakness, weak cry	Facial paralysis, dysarthria, dysphagia	Respiratory distress, progressive muscle weakness	Fever, respiratory distress, dysphagia, weight los	Stridor, dysphagia, fever, drooling, ptosis	Hearing loss, facial paralysis, drooling, and drooping eyelid
Respiratory involvement	Yes, severe (required mechanical ventilation)	Yes, severe (required mechanical ventilation)	Yes (required mechanical ventilation)	Yes (required mechanical ventilation)	Yes (received different modalities of ventilatory support)	No
EMG findings	Motor axonal neuropathy	Reduced CMAP amplitude, decreased motor NVC in upper extremities	Reduced CMAP amplitude	Axonal sensorimotor polyneuropathy	Axonal sensorimotor polyneuropathy	Normal
Riboflavin dose	10 mg/kg/day	60 mg/kg/day	15 mg/kg/day	80 mg/kg/day	80 mg/kg/day	10-15 mg/kg/day
Response to riboflavin	No	Yes	Yes	Yes	Yes	Yes
Clinical outcome	Death	Stabilization and improvement	Slow stabilization	Gradual improvement	Improvement	Gradual improvement

Data were extracted from previously published reports.
EMG: electromyography; CMAP: compound muscle action potential; NCV: nerve conduction velocity.

as a variety of cranial nerve paralysis that mainly affects cranial nerves VII, IX, and XII, resulting in clinical manifestations of dysphagia, dysarthria, and facial weakness. It may also affect cranial nerve II, leading to symptoms such as decreased visual acuity, visual field atrophy, and even color blindness. It rarely affects the V nerve, affecting functions such as chewing and speaking, and the III and VI nerves, bringing with it impairment in eye movement.[14] Muscle weakness and hypotonia are prominent, particularly in the axial and upper limb muscles.[15] Among the most severe signs, respiratory compromise secondary to neurogenic paralysis can be seen.

Diagnosis

The diagnosis of RTD is based on clinical findings such as cranial neuropathy characterized by bulbar palsy, motor neuropathy, and sensory neuropathy manifested by ataxia and alteration in vibration and proprioception,[6] as well as neurophysiological findings such as electromyography, nerve action potentials, audiometry, and electroencephalogram. It can be supported by MRI where some cases report cerebellar atrophy. In supportive laboratory tests like blood acylcarnitine profiles and identification of biallelic pathogenic variants in SLC52A2 or SLC52A3 in molecular genetic tests that may include a combination of gene-targeted tests (multigene panel) and comprehensive genomic tests (exome sequencing, genome sequencing) according to the phenotype.[6,16,17]

Treatment

The treatment of this syndrome consists of RF supplementation of 10-50 mg/kg/day,[15] which should be

started from clinical suspicion, even without confirmation of the diagnosis.[18] The effective response to supplementation depends on various factors, such as the degree of damage to the transporters. Timely treatment can decrease or reverse the symptoms already presented; conjunctive therapy with antioxidants such as CoQ10 can be used in the management of RTD.[19]

Discussion

In comparison with previously reported cases in the literature (Table 1), the most frequent clinical manifestations in affected infants include dysphagia and hypotonia. In addition, the majority of patients develop significant respiratory involvement, which represents a major complication and an important marker of poor prognosis.

Cases associated with missense variants generally exhibit a more favorable therapeutic response to high-dose RF supplementation, likely due to the preservation of partial residual transporter function. This contrasts with the case presented in this report, in which no clinical improvement was observed despite adequate RF supplementation. These findings underscore the relevance of the degree of transporter dysfunction, as both the type and the location of the pathogenic variant appear to be key determinants of therapeutic response. Among the reviewed cases reported in the literature,[20-27] no nonsense variants comparable to that identified in our patient were observed.

Although the variant has been deposited in ClinVar, this represents the first detailed clinical report with comprehensive phenotypic characterization. Pathogenic variants in SLC52A3 are less prevalent than those reported in SLC52A2 in RTD.

Consistently, a previous study reported that nonsense variants in SLC52A3 account for approximately 2% of cases,[27] highlighting the rarity of the presentation observed in our patient. This type of variant likely contributes to the poor response to RF therapy, particularly when associated with delayed diagnosis. Analysis of previously published cases reveals marked heterogeneity in clinical presentation and prognosis, which may be related to specific genetic variants and, potentially, to additional modifying mechanisms that remain incompletely understood.

Our findings emphasize the importance of early genetic diagnosis in patients with suspected RTD, as variant-specific differences may influence prognosis and therapeutic response, particularly to RF supplementation.

Conclusion

RTD should be considered in pediatric patients with progressive neuromuscular symptoms. Early clinical suspicion is crucial to initiate timely treatment; however, this case illustrates that response to RF supplementation may be poor in the presence of severe loss-of-function mutations, highlighting the importance of genotype-phenotype correlations for prognosis and clinical counseling.

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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. 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. The authors declare that ChatGPT was used exclusively to improve the language, grammar, and clarity of the manuscript.

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ORIGINAL ARTICLE

Concordance of repetitive nerve stimulation test at low frequencies and AChR in myasthenia gravis

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Abstract

Objective: *The objective of the study was to determine diagnostic concordance between repetitive nerve stimulation test at low frequencies (LF-RNST) and anti-nicotinic acetylcholine receptor (AChR) in myasthenia gravis (MG).* **Methods:** *We performed a retrospective longitudinal observational concordance study. After authorizing the protocol of the Physical Medicine and Rehabilitation service patient registry, the clinical records that met the selection criteria were selected, and the following variables were recorded: positive LF-RNST, negative LF-RNST, negative AChR, positive AChR, diagnosis of confirmed MG, and diagnosis of ruled out MG.* **Results:** *A total of 106 records were included in this study, with an unweighted Cohen's kappa coefficient agreement of 0.952, a 95% confidence interval for patients with both positive tests and a confirmed diagnosis of MG, and an unweighted Cohen's kappa coefficient of 0.544, a 95% confidence interval for patients with both negative tests and a diagnosis of discarded MG.* **Conclusions:** *The LF-RNST could be very similar to the AChR test if performed in patients with MG.*

Keywords: *Myasthenia gravis. Electrodiagnostic testing. Repetitive stimulation.*

Concordancia de la prueba de estimulación nerviosa repetitiva a bajas frecuencias y AChR en la miastenia gravis

Resumen

Objetivo: *Determinar la concordancia diagnostica de la PERNBF con los AChR en miastenia gravis.* **Métodos:** *Mediante un estudio de concordancia retrospectivo longitudinal observacional y posterior a la autorización del protocolo del registro de pacientes del servicio de Medicina Física y Rehabilitación se seleccionaron los expedientes clínicos que cumplieron con los criterios de selección registrando las siguientes variables: PERNBF positiva, PERNBF negativo, AChR negativa, AChR positiva, diagnóstico de MG confirmado, diagnóstico de MG descartado.* **Resultados:** *Un total de 106 expedientes fueron incluidos en este estudio, presentaron una concordancia por coeficiente de kappa de Cohen no ponderada de 0.952, con un intervalo de confianza del 95% para los pacientes con ambas pruebas positivas y diagnóstico confirmado de MG y un coeficiente kappa de Cohen no ponderada de 0.544, con un intervalo de confianza del 95% para los pacientes con ambas pruebas negativas y diagnóstico de MG descartado.* **Conclusiones:** *La PERNBF podría ser muy similar a la prueba de AChR en caso de realizarse a pacientes enfermos de MG.*

Palabras clave: *Myasthenia gravis. Electrodiagnostic testing. Repetitive stimulation.*

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Introduction

The low-frequency repetitive nerve stimulation test (LF-RNST) in the clinical neurophysiology laboratory is a useful diagnostic tool for postsynaptic neuromuscular junction diseases, such as myasthenia gravis (MG). In addition to its diagnostic utility, it has been proposed as a possible independent predictor of the progression from ocular myasthenia to generalized MG.[1] Its diagnostic performance has been widely documented, with reported sensitivity between 30% and 80%[2] and specificities ranging from 76.9% to 97%, depending on the type of clinical presentation and the stage of the disease.[2,3]

MG is a chronic autoimmune disease that affects the neuromuscular junction at the postsynaptic level, in which antibodies against the nicotinic acetylcholine receptor (AChR) play a central role in the pathophysiology[3]. Clinically, MG is characterized by fluctuating muscle weakness and fatigability, with symptoms becoming more pronounced toward the end of the day. It can present as oculobulbar, with ptosis and diplopia, or as generalized, primarily affecting proximal muscles and even respiratory muscles in the most severe cases[4,5].

The diagnosis of MG is based on the integration of clinical assessment, serological studies, and electrodiagnostic tests. Among the available studies are antibodies against the specific muscle tyrosine kinase receptor, which can be positive in a significant percentage of patients seronegative for aChR[3], single-fiber electromyography, with reported sensitivities between 86% and 92% and specificities between 70% and 98%[3], and PERNBF. Antibodies against low-density lipoprotein receptor-related protein 4 (LRP4) and AGF have also been described in double-seronegative patients[6]. Antibodies against the arachidonic acid receptor (AChR) have a specificity close to 100% and are found in 80-90% of patients with generalized MG[3,4], making them one of the main reference diagnostic tools. Low-frequency repetitive nerve stimulation test (LF-RNST) is the most widely used electrodiagnostic method for evaluating neuromuscular transmission[7]. It is performed by stimulating at low frequencies, generally within a range of 1-5 Hz[8], under specific technical conditions such as body temperature control, adequate muscle immobilization, and the application of bursts of supramaximal stimuli[9,10]. This study can demonstrate a progressive and reproducible decrease in the amplitude of compound muscle action potential, characteristic of neuromuscular transmission disorders.

Although numerous studies have evaluated the sensitivity and specificity of LF-RNST, information on the diagnostic agreement between this electrophysiological test and anti-AChR antibody titration is limited. Determining the degree of agreement between these two tools could provide relevant clinical information regarding the diagnostic weight of each test and its usefulness in different clinical scenarios.

Therefore, the objective of this study was to determine the diagnostic agreement between RNNSS and anti-AChR antibody titration in patients evaluated for suspected MG. Cut-off point, which is shared by most of the bibliography reviewed in this article, is ≥ 10%.

Methods

This was a retrospective, longitudinal, observational concordance study in which clinical records were collected from the database from our institution for patients with suspected MG who were referred to the Physical Medicine and Rehabilitation service, specifically the electrodiagnostics area, for LF-RNST testing between August 2010 and September 2023. The definitive diagnosis of MG (confirmed or ruled out) was established by the Neurology service and recorded in the clinical record, based on the patient's comprehensive clinical evaluation and available complementary studies, including AChR antibody titers. This neurological clinical diagnosis was considered the reference standard for the concordance analysis.

Patient records were selected from those with a PERNBF report and available results for AChR antibody titer, as this test was used as the reference standard for concordance analysis between the two diagnostic tools. Patients evaluated with other antibodies associated with MG, such as anti-muscle-specific kinase (MuSK) or LRP4, were systematically excluded.

The following variables were collected for statistical analysis: sex, age, positive and negative PERNBF results, positive and negative AChR results, and the final diagnosis recorded by Neurology as confirmed or ruled-out MG.

LF-RNST studies were performed in the electrodiagnostic laboratory using a Nihon Kohden Neuropack S3 electromyography system, following the service's standardized protocol. Before the study, the temperature of the limb being evaluated was maintained at approximately 33°C, and the muscle to be examined was immobilized to optimize recording. Initially, routine motor conduction studies were performed to verify peripheral nerve integrity.

Subsequently, repetitive nerve stimulation was applied at rest at a frequency of 3 Hz using bursts of 5-10 supramaximal stimuli. The procedure was repeated 3 times with approximately 1-min intervals. Clinically relevant muscles were evaluated according to the distribution of weakness in each patient, focusing on proximal, distal, or facial muscles based on clinical suspicion.

The LF-RNST was considered positive when a decrease of 10% or more in the amplitude of the compound muscle action potential was documented between the first and fourth or fifth responses within the same stimulation burst. This cutoff point was used uniformly in the interpretation of the included studies, in accordance with the electrodiagnostic criteria routinely employed in the laboratory.

In cases with significant decreases, complementary maneuvers were performed consisting of brief maximal voluntary exercise followed by immediate repetitive stimulation to assess post-exercise facilitation or restitution, according to the service's standard protocol.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 24 software. Cohen's unweighted kappa coefficient was calculated to evaluate the agreement between the PERNBF and the AChR test in patients with a confirmed diagnosis of MG and in those with a ruled-out diagnosis. Descriptive statistics of patient age were also obtained, including mean, median, and mode.

The study was approved by the ethics, research, and biosafety committees of the Centro Médico Nacional 20 de Noviembre, registration number 305.2024.

Table 1. Characteristics of the population studied

Characteristic	Age and sex
n	106
Female	70
Male	36
Mode	49.000[a]
Media	47.755
Median	51.000
Standard deviation	20.410
Minimum	1.000
Maximum	81.000

n: total patients.

Table 2. Cohen's unweighted kappa in patients with both positive tests

Qualifiers	Unweighted Kappa	SE	95% CI	
			Lower	Upper
Average kappa	0.952			
RNST-LF - AChR	0.952	0.048	0.859	1.000

59 study subjects with both positive tests and MG carrier.
RNST-LF: repetitive nerve stimulation test at low frequencies; AChR: anti-nicotinic acetylcholine receptor antibodies; CI: confidence interval; SE: standard error.

Results

A total of 106 records were included in this study, of which 70 were from women and 36 to male patients (Table 1). The minimum age was 1 year, and the maximum age was 81 years, with a mode of 49 years, a mean of 47.75, and a median of 51 years with a standard deviation of 20.4 (Table 1). Regarding the agreement of the two evaluators, with the number one evaluator in this study being the LF-RNST and the number two evaluators of the AChR test, they presented an unweighted Cohen's kappa coefficient agreement of 0.952, with a lower limit of 0.859 and an upper limit of 1.00, presenting a standard error of 0.048 with a 95% confidence interval for patients with both positive tests and a confirmed diagnosis of MG (Table 2). An unweighted Cohen's kappa coefficient of 0.544 was found, with a lower limit of 0.099 and an upper limit of 0.988, presenting a standard error of 0.227 with a 95% confidence interval for patients with both negative tests and a diagnosis of discarded MG (Table 3). The diagnostic yield of LF-RNST presented a positive predictive value of 90.1%, a negative predictive value of 76.3%, a sensitivity of 77.9%, and a specificity of 89.3% in 106 patients who underwent LF-RNST (Table 4).

Discussion

This study yielded similar results regarding the disease's behavior to those described in the existing literature, showing a predominance of females[3], as well as mean, mode, and median ages at the time of the PERNBF test relatively close to those described in populations from European countries[4].

Regarding the diagnostic performance of the PERNBF test, its sensitivity and specificity remained within the ranges described in the literature[2,3], as did the positive and negative predictive values of 90% and

Table 3. Cohen's unweighted kappa in patients with both negative tests

Qualifiers	Unweighted Kappa	SE	95% CI	
			Lower	Upper
Average kappa	0.544			
RNST-LF - AChR	0.544	0.227	0.099	0.988

47 study subjects with both negative tests and not carrying MG.
RNST-LF: repetitive nerve stimulation test at low frequencies; AChR: anti-nicotinic acetylcholine receptor antibodies; CI: confidence interval; SE: standard error.

Table 4. Diagnostic performance of RNST-LF

Parameter	%
Predictive value+	90.1
Predictive value–	76.3
Sensitivity	77.9
Specificity	89.3

Data expressed as a number (%).
RNST-LF: repetitive nerve stimulation test at low frequencies.

76%, respectively, obtained in this study. These findings are consistent with previous reports and support the role of the PERNBF test as a useful tool in the diagnostic approach to neuromuscular transmission disorders.

As for concordance, a very high result was obtained, with a Cohen's kappa coefficient of 0.952 when both tests were positive and a confirmed diagnosis of MG was present. In contrast, for cases where both tests were negative and the diagnosis of MG was ruled out, the agreement was moderate, with a Cohen's kappa coefficient of 0.544.

These results suggest that when the AChR test is positive and the patient has MG, the PERNBF test shows very good agreement with positive results, reinforcing its usefulness as a complementary study in the appropriate clinical context. On the other hand, in patients without the disease and with a negative AChR test, moderate agreement suggests greater variability in the PERNBF results, which may be influenced by factors such as the clinical distribution of weakness, the muscle evaluated, the stage of the disease, and the technical conditions of the study.

It is thought that this behavior can be explained by the fact that the PERNBF test is highly specific and has a high positive predictive value, making it comparable to the AChR test when evaluating patients with established disease. However, its sensitivity can vary depending on the clinical presentation, being lower in ocular forms and higher in generalized forms, as previously described in the literature[2,3].

When comparing these findings with other diagnostic modalities, single-fiber electromyography has been described as the most sensitive electrophysiological method for evaluating neuromuscular transmission; however, its availability is limited and largely depends on the operator's experience. In this context, single-fiber percutaneous neuromuscular fibrillation remains an accessible and highly useful tool in everyday clinical practice, especially in centers where other more specialized techniques are unavailable.

It is important to consider that MG is a heterogeneous entity and that a subgroup of patients may be seronegative for antibodies against the AChR and positive for other antibodies, such as anti-MuSK or LRP4[6]. These subgroups were not specifically evaluated in the present study, so the results should be interpreted primarily in the context of patients evaluated by AChR titration.

Finally, although the PERNBF showed good diagnostic performance and high agreement with the AChR test in positive cases, further studies, ideally prospective, are required to reduce possible methodological biases and more accurately evaluate the behavior of this test in different clinical subgroups of patients with suspected MG.

Limitations

The greatest limitation of this study is that it was retrospective; therefore, it was not possible to verify an adequate and the same technique for all patients who underwent the test, in addition to not being present to observe the muscle uptake for each patient and the cut-off point that was used to report the LF-RNST as positive.

Conclusion

The PERNBF test shows good concordance with the AChR antibody test in patients with MG evaluated by AChR titration. Therefore, it can be considered a useful complementary diagnostic tool, especially in healthcare centers where serological studies are unavailable but electrodiagnostic equipment and trained personnel are available when MG is clinically suspected.

These findings should be interpreted primarily in the context of patients evaluated with AChR antibodies, as seronegative subgroups, such as those with anti-MuSK or LRP4 antibodies, were not specifically analyzed. Therefore, the PERNBF test should be considered part of a comprehensive diagnostic approach and not an absolute substitute for serology.

Finally, it is necessary to develop accessible diagnostic strategies for the evaluation of MG at different levels of care, as well as to continue exploring new complementary diagnostic tools, such as videonystagmography, due to its greater tolerance by the patient and less dependence on the operator compared to traditional electrodiagnostic methods[11].

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

Conflicts of interest

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ORIGINAL ARTICLE

Self-perceived stigma in Parkinson's disease: a longitudinal cohort study

*Ana L. Guerra-Anzaldo, Germán Rivera-Monroy, Amin Cervantes-Arriaga, Karen I. Sánchez-Ramírez, Ariadna Domínguez-García, and Mayela Rodríguez-Violante**

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Abstract

Objective: *This study aimed to evaluate changes in stigma over 1 year among people with Parkinson's disease (PwP).* **Methods:** *A longitudinal, observational study was conducted. Data were collected at 2 time points: baseline and at a 1-year follow-up visit. Demographic and clinical data were collected, including disease severity, motor and non-motor symptoms severity and health-related quality of life. Stigma was assessed using the corresponding subdomain of the 39-item PD Questionnaire.* **Results:** *A total of 117 PwP were included (55.6% male; mean age 61.9 ± 12.4 years). After a mean follow-up of 12.8 months, significant improvements were observed in motor symptoms, mobility, and activities of daily living. Stigma levels remained largely unchanged overall, with only 29.1% of participants showing improvement. This group had greater reductions in non-motor symptoms and total Movement Disorder Society-Unified PD Rating Scale scores compared to those with no change or worsening. Multivariate analysis identified changes in perceived social support and presence of anxiety as significant predictors of stigma improvement (p = 0.02 and p = 0.03, respectively).* **Conclusions***: While clinical improvements were observed over 1 year, self-perceived stigma remained mostly unchanged. Improvement in stigma was associated with better patient-reported outcomes and linked to lower anxiety and better perceived social support. These findings show the importance of integrating psychosocial strategies into PD care to address stigma effectively.*

Keywords: *Parkinson's disease. Social stigma. Quality of life.*

Estigma percibido en la enfermedad de Parkinson: un estudio de cohorte longitudinal

Resumen

Objetivo: *Evaluar los cambios en el estigma a lo largo de un año en personas con enfermedad de Parkinson (PwP).* **Métodos:** *Se realizó un estudio longitudinal y observacional. Los datos se recopilaron en dos momentos: al inicio y en una visita de seguimiento un año después. Se obtuvieron datos demográficos y clínicos, incluyendo la gravedad de la enfermedad, la severidad de los síntomas motores y no motores, y la calidad de vida. El estigma se evaluó utilizando el subdominio correspondiente del Cuestionario de Parkinson de 39 ítems (PDQ-39).* **Resultados:** *Se incluyeron 117 PwP (55.6% hombres; edad promedio 61.9 ± 12.4 años). Tras un seguimiento promedio de 12.8 meses, se observaron mejoras significativas en los síntomas motores, la movilidad y las actividades de la vida diaria. Los niveles de estigma permanecieron en gran medida sin cambios, y solo el 29.1% de los participantes mostró mejoría. Este grupo presentó mayores reducciones en los síntomas*

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no motores y en los puntajes totales de la MDS-UPDRS en comparación con aquellos sin cambio o con empeoramiento. El análisis multivariado identificó los cambios en el apoyo social percibido y la presencia de ansiedad como predictores significativos de la mejoría del estigma (p = 0.02 y p = 0.03, respectivamente). **Conclusiones:** *Aunque se observaron mejoras clínicas, el estigma autopercibido permaneció mayormente sin cambios. La mejoría se asoció con menor ansiedad y mejor apoyo social percibido. Estos hallazgos resaltan la importancia de integrar estrategias psicosociales en la atención de la enfermedad.*

Palabras clave: *Enfermedad de Parkinson. Estigma social. Calidad de vida.*

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with a slow onset and heterogeneous manifestations, affecting more than six million people worldwide and ranking as the second most prevalent neurodegenerative condition.[1] Clinically, PD is characterized by bradykinesia, rigidity, and resting tremor, resulting from chronic degeneration of dopaminergic neurons in the substantia nigra. This neuronal loss leads to motor disturbances and non-motor symptoms.[2] Stigma is a multidimensional construct that includes enacted (social) stigma, internalized stigma, and self-perceived (felt) stigma, which reflects the individual's subjective experience of being stigmatized. Alongside the complexities of motor and non-motor symptoms, people living with PD (PwP) face the burden of self and social stigma. In healthcare settings, stigma arises from misconceptions and negative attitudes toward medical conditions, often leading to marginalization and reduced recognition of patients as individuals.[3] This study aimed to evaluate changes in self-perceived stigma in PwP over 1 year.

Methods

A longitudinal, observational study was conducted to evaluate changes in self-perceived stigma over 1 year among PwP. PD diagnosis was confirmed by a movement disorders specialist using the Movement Disorders Society clinical criteria.[4] The exclusion criteria included subjects with alternative neurodegenerative disorders, significant cognitive impairment that obstructed understanding of the study procedures, or any condition that, in the investigator's assessment, could have interfered with study participation or the interpretation of results.

The study was approved by the Institutional Review Board. Informed consent was obtained from all participants before their enrollment in the study.

Data were collected at 2 time points: baseline and at a 1-year follow-up visit. Demographic information was obtained from each participant, including age and sex. Clinical data included age of onset, disease duration, levodopa equivalent daily dose, disease severity (through the Hoehn and Yahr stages [HY]), and motor symptoms severity as measured by the Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS). Health-related quality of life (HR-QoL) was assessed with the 39-item PD Questionnaire (PDQ-39).

The MDS-UPDRS is a comprehensive tool utilized for the clinical assessment of PD and is divided into four parts: Part I evaluates non-motor experiences of daily living, Part II assesses motor experiences of daily living, Part III focuses on motor examination, and Part IV gauges motor complications. Each section is scored on a scale, where the majority of items are rated from 0 (normal) to 4 (severe), providing a detailed overview of both motor and non-motor symptoms associated with PD. The MDS-UPDRS has been validated for its reliability, sensitivity to change, and specificity.[5]

The HY is a widely utilized clinical rating system for the classification of the progression of PD, describing the progression of PD symptoms in five stages, from Stage 1 (unilateral involvement only, minimal or no functional impairment) to Stage 5 (wheelchair-bound or bedridden unless aided).[6]

The PDQ-39 is a well-established tool intended to assess HRQoL in PwP, with 39 items over eight dimensions: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and physiological discomfort. The self-perceived stigma domain explicitly examines the perceived social and internal stigmatization encountered by PwP, highlighting the effects of PD on social interactions and personal identity. Each item on the PDQ-39 is scored on a scale from 0 (never) to 4 (always), with the scores transformed into a 0-100 scale for each domain, where a higher score indicates a worse level of functioning or well-being.[7] The PDQ-39 stigma domain was utilized to assess changes in stigma levels.

The Hamilton Anxiety Rating Scale (HARS) consists of 14 items, each rated on a scale from 0 (not present)

to 4 (very severe).[8] The Hamilton depression rating scale (HDRS) incorporates 17 items evaluating various aspects of depression. Each item is rated on a scale of 0-2 or 0-4, with higher scores indicating greater severity.[9]

Statistical analysis

Initial analyses included descriptive statistics for all variables at baseline and the 1-year follow-up visit. The primary analysis was focused on the change in PDQ-39 self-perceived stigma scores from baseline to the 1-year follow-up. A paired t-test was used to assess the significance of this change for normally distributed data, whereas a non-parametric alternative was used for non-normal data.

For each participant, the stigma change score was calculated as the follow-up PDQ-39 self-perceived stigma domain score minus the baseline score. Positive change scores indicated improvement in self-perceived stigma, negative scores indicated worsening, and a change score of zero indicated no change.

Participants were categorized accordingly into two groups (improved, worsened or unchanged self-perceived stigma), and the proportion of participants in each category was calculated. Improvement in stigma was treated as the outcome of interest in subsequent analyses, and odds ratios with 95% confidence intervals (CI) were estimated to identify factors associated with stigma improvement.

Multivariable linear regression analysis was conducted to examine the impact of significant variables on the change in PDQ-39 self-perceived stigma scores. To estimate the likelihood of stigma improvement, logistic regression models were employed, treating improvement as a binary outcome (1 = improvement, 0 = no change or worsening). The overall statistical significance of the model was assessed using the Likelihood Ratio (LLR) test. The model's explanatory power was evaluated using the Pseudo R-squared (R^2), and further model fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Statistical significance was considered $p < 0.05$.

Results

A total of 117 PwP (55.6% male) were included. The mean age was 61.9 ± 12.4 years. The mean disease duration was 7.4 ± 5 years. At baseline, the mean HY stage was 2.3 ± 0.8 with a mean score in the MDS-UPDRS part 3 of 33.2 ± 16.7 points. The mean time between visits was 12.8 months (median 12).

The mean scores of the main scales and their comparisons between visits for the complete study sample are shown in table 1. Overall, improvements were observed between visits in the MDS-UPDRS 3 score (mean difference 4.3 ± 1.5, p = 0.01), MDS-UPDRS total score (mean difference 6 ± 2.2, p = 0.01), PDQ-39 mobility (mean difference 4 ± 2.4, p = 0.03), and PDQ-39 activities of daily living (mean difference 5.8 ± 2.4, p = 0.01). Conversely, there was a trend for deterioration in PDQ-39 social support (mean difference 2.5 ± 1.9, p = 0.07).

Concerning stigma within the complete sample, there was a marginal decline in the domain index of 0.5 ± 2.2 points, which did not achieve statistical significance (p = 0.43). Overall, 29.1% (n = 34) had an improvement in the self-perceived stigma domain index, whereas 70.9% (n = 83) showed worsening or remained unchanged.

On the other hand, when analyzing PwP showing improvement in self-perceived stigma, significant reductions in patient-related outcomes compared to those with no change or worsening were found. Specifically, the improvement group had a greater decrease in the MDS-UPDRS total scores compared to the worsening/no-change group (p = 0.001), with parts 1 and 2 also showing differences (p = 0.02 and p = 0.001, respectively). No differences were found regarding MDS-UPDRS part 3 (p = 0.09). In addition, a statistically significant improvement in HDRS and HARS was found. Table 2 presents the complete data.

Based on the VIF analysis, the variables with extremely high multicollinearity (VIF > 10) were excluded from the multivariate logistic regression. Since the individual PDQ-39 indices represent distinct dimensions, each with unique theoretical relevance or differential empirical associations with the outcomes, retaining these separate measures within the model offered additional insights and was included in the model.

The final logistic regression model, estimated on 117 observations with 15 predictors, was statistically significant (LLR, p = 0.001) and explained approximately 26% of the variance in the outcome (Pseudo $R^2 = 0.264$). Overall, the model fit indices (AIC = 135.81, BIC = 180.00, and Log-Likelihood = –51.90) indicate an acceptable fit compared to the null model (LL-Null = –70.51).

Among all predictors, two variables emerged as statistically significant. The regression coefficient for the delta index for social support was 0.04 (p = 0.02), which

Table 1. Comparison of the main scales between baseline and follow-up visits

Variable	Baseline (mean ± SD)	Follow-up (mean ± SD)	p
MDS-UPDRS I	9.5 ± 5.9	9 ± 6.2	0.48
MDS-UPDRS 2	12.1 ± 8.3	11.1 ± 8.2	0.17
MDS-UPDRS 3	33.2 ± 16.7	29 ± 14.7	0.01
MDS-UPDRS 4	2.2 ± 3.7	2.1 ± 3.4	0.65
MDS-UPDRS Total	57.2 ± 26.3	51.2 ± 26.4	0.01
HDRS	7.6 ± 6.4	7.7 ± 6	0.96
HARS	7.4 ± 6.9	7.3 ± 6.2	0.90
EQ-5D	5 ± 3.5	4.8 ± 4.2	0.63
PDQ-39 mobility	29 ± 21.7	24.7 ± 22.4	0.03
PDQ-39 activities of daily living	25.2 ± 21.6	19.4 ± 20.3	0.01
PDQ-39 emotional well-being	19.5 ± 18.1	16.7 ± 19.6	0.20
PDQ-39 stigma	11.1 ± 19.9	11.5 ± 18.1	0.44
PDQ-39 social support	6.6 ± 15.1	9.1 ± 15.3	0.07
PDQ-39 cognitions	16.4 ± 15.7	16.5 ± 17.2	0.95
PDQ-39 communication	14.7 ± 18.9	14 ± 17.4	0.90
PDQ-39 bodily discomfort	17.9 ± 18.7	16.6 ± 18.8	0.43
PDQ-39 summary index	20.4 ± 13.4	17.8 ± 14.2	0.09

MDS-UPDRS: Movement Disorder Society - Unified Parkinson's disease rating scale; HDRS: Hamilton depression rating scale; HARS: Hamilton Anxiety Rating Scale; EQ-5D: EuroQol 5 dimensions; PDQ-39: Parkinson's disease questionnaire-39 items; SD: standard deviation.

translates to an odds ratio (OR) of 1.04 (95% CI: 1.01-1.08). The coefficient for the reduction of anxiety score was –1.6 (p = 0.03), corresponding to an OR of 0.2 (95% CI: 0.05-0.86). The remaining predictors did not reach statistical significance, suggesting that, in the presence of the other variables, they do not independently predict the outcome.

Discussion

Self-perceived stigma is a dynamic construct influenced by individual beliefs and experiences, as well as factors such as disease severity, disease duration, and social support networks.[10] Several studies have focused on identifying the primary factors that lead to the stigma surrounding PD. Sociodemographic characteristics, including age and gender, as well as the severity of motor symptoms, are often considered determinants of stigma. Vulnerable groups, including the elderly, women, and those displaying significant motor manifestations, are particularly prone to stigma.[11,12] However, emerging evidence suggests that self-perceived stigma may not directly parallel motor symptom burden and may instead reflect more stable psychosocial and identity-related constructs. Importantly, changes in self-perceived stigma may occur independently of changes in enacted or internalized stigma, underscoring the necessity of longitudinal follow-up on PwP mental health concerning this issue.[13]

In this longitudinal observational study, we aimed to assess the change of self-perceived stigma over 1 year in PwP, while also examining the role of motor and non-motor symptoms. While stigma levels remained largely unchanged, only a third of the PwP showed improvement in the stigma domain, with the rest either worsening or remaining stable. This finding highlights that improvements in clinical status do not uniformly translate into reductions in self-perceived stigma. In the PwP group showing a reduction in self-perceived stigma, modest but statistically significant improvements were observed over an average follow-up of 12 months in motor symptoms (MDS-UPDRS parts 3

Table 2. Comparison of the main scales between No change/Worsening and Improvement according to the stigma

Variable	No change/worsening (n = 83)	Improvement (n = 34)	p
Female (%)	33 (39.8)	19 (55.9)	0.16
Employment basal (%)	49 (59)	25 (73.5)	0.41
Age	63 ± 12.7	58.6 ± 11.1	0.06
Years of education	10.8 ± 5.5	11.1 ± 4.1	0.78
Disease duration	7.3 ± 5.3	7.2 ± 4.4	0.91
MDS-UPDRS total basal	54 ± 24.6	64.8 ± 29	**0.03**
MDS-UPDRS total follow-up	52.9 ± 26.9	48 ± 25.2	0.37
Δ MDS-UPDRS total	−1.6 ± 21.7	−16.7 ± 27.1	**0.001**
MDS-UPDRS 1 basal	8.8 ± 5.5	11.2 ± 6.7	0.07
MDS-UPDRS 1 follow-up	9.3 ± 6.1	8.3 ± 6.6	0.32
Δ MDS-UPDRS 1	0.5 ± 6.8	−2.9 ± 7.9	**0.02**
MDS-UPDRS 2 basal	11.2 ± 7.9	14.6 ± 9	0.06
MDS-UPDRS 2 follow-up	11.7 ± 8.4	9.7 ± 7.7	0.16
Δ MDS-UPDRS 2	0.4 ± 7.8	−4.9 ± 9.2	**0.002**
MDS-UPDRS 3 basal	32.1 ± 16.3	36 ± 17.4	0.19
MDS-UPDRS 3 follow-up	29.5 ± 14.8	27.6 ± 14.8	0.37
Δ MDS-UPDRS 3	−2.6 ± 14.3	−8.4 ± 19.2	0.09
MDS-UPDRS 4 basal	1.9 ± 3.6	2.9 ± 3.8	**0.03**
MDS-UPDRS 4 follow-up	2.4 ± 3.4	2.4 ± 3.4	0.25
Δ MDS-UPDRS 4	0.1 ± 3.8	−0.5 ± 4.1	0.11
HDRS basal	6.5 ± 5.2	10.5 ± 8.2	**0.01**
HDRS follow-up	8 ± 6.1	7 ± 5.7	0.46
Δ HDRS	1.5 ± 7.7	−3.5 ± 7.9	**0.002**
HARS basal	6.3 ± 6	10.1 ± 8.2	**0.01**
HARS follow-up	7.4 ± 6	7 ± 6.7	0.46

Bold text denotes statistically significant differences ($p < 0.05$).
Δ: indicates change calculated as follow-up minus baseline score.
MDS-UPDRS: Movement Disorder Society - unified parkinson's Disease Rating Scale; HDRS: hamilton depression rating scale; HARS: Hamilton Anxiety Rating Scale;

and total), PDQ-39 mobility, and PDQ-39 activities of daily living. However, the magnitude of motor improvement alone was insufficient to explain stigma change, suggesting that motor recovery is not the primary driver of stigma reduction.

Those who improved in self-perceived stigma also experienced greater reductions in MDS-UPDRS parts 1 and 2, and in depression and anxiety scores, suggesting a stronger link between self-perceived stigma and non-motor, patient-reported outcomes. These findings align with prior research showing that emotional well-being and functional status are tightly intertwined with stigma in PD. For example, people with more depressive symptoms tend to report higher stigma. Conversely, improvements in mood, anxiety, and perceived social functioning may play a more central role in self-perceived stigma change than motor improvement alone.[14]

Consistent with this interpretation, the multivariate logistic regression model identified that better perceived social support and less anxiety were independently associated with an improvement in self-perceived stigma

at follow-up. In contrast, motor variables did not retain independent significance. This reinforces the concept that self-perceived stigma is relatively independent of motor symptom severity and more closely related to psychosocial context and emotional state. Each unit decrease in the PDQ-39 social support score, indicating better perceived support, was associated with approximately a 4% increase in the odds of stigma improving. On the other hand, reductions of anxiety were associated with an approximately 80% higher likelihood of stigma improvement.

These results have important implications. They reinforce the notion that while PD interventions may improve clinical symptoms and certain quality-of-life aspects, self-perceived stigma may persist unless psychosocial and emotional dimensions are directly addressed. The effect of changes in perceived social support highlights a need for targeted psychosocial interventions, such as education programs or support groups, to complement clinical treatment. Such multifaceted approaches could further alleviate the burden of stigma and potentially catalyze broader improvements in both motor and non-motor symptoms. Our observation that increased social support and reduced anxiety accompany stigma improvement suggests that targeted psychosocial interventions could be beneficial. For instance, education programs, support groups, and counseling services might be introduced as routine parts of PD care to help PwP and families cope with stigma, build supportive networks, and address fears or misconceptions. Recent literature strongly echoes this approach.[15] Notably, Spagna et al. observed a decline in perceived social support after deep-brain stimulation, despite improvements in motor function and quality of life. This finding further illustrates that emotional and social well-being, and by extension self-perceived stigma, may not improve in parallel with physical outcomes, underscoring the importance of stigma-focused interventions in PD care.[16]

Several limitations should be considered when interpreting these results. First, as a longitudinal observational study, causality cannot be established. While we observed associations between improvements in MDS-UPDRS, depression and anxiety scores, we cannot definitively say that clinical improvements caused reductions in perceived stigma.

Second, this was a single-center study, and although the sample size of 117 participants was adequate for detecting longitudinal changes, the lack of a multicenter design may limit the representativeness and external validity of the findings, particularly given the clinical, cultural, and healthcare-system heterogeneity of PD across settings. Future multicenter studies would enhance generalizability and allow evaluation of contextual influences on self-perceived stigma.

Another important limitation is the reliance on self-reported measures, such as the PDQ-39 stigma domain, which may be influenced by individual perceptions, mood state, and response bias. Although widely used, the PDQ-39 is not a stigma-specific instrument and captures only a limited, subjective dimension of stigma. This domain may be subject to ceiling and floor effects, particularly in PwP with very low or very high baseline stigma scores, potentially limiting its sensitivity to detect subtle longitudinal changes. These measurement characteristics may partly explain the relative stability of stigma observed over the follow-up period, despite improvements in several motor and non-motor outcomes. Future studies should consider incorporating more disease-specific tools, such as the PwP Stigma Questionnaire (PDStigmaQuest), to improve measurement precision and to allow a more comprehensive and responsive assessment of multiple stigma dimensions.

The follow-up period of 1 year, while sufficient to detect short-term changes, may not adequately capture long-term trajectories of perceived stigma or the durability of clinical improvements. Extending follow-up to 2-3 years would allow assessment of sustained stigma changes and their relationship with disease progression and treatment adaptations.

Finally, important potential confounders were not fully accounted for, including pharmacological treatment characteristics (e.g., dopaminergic dose and medication adjustments), advanced therapies, and surgical interventions, as well as structured psychosocial or social support interventions. Future studies should systematically incorporate these variables to better control for their influence on perceived stigma and to disentangle clinical from treatment-related effects.

Conclusion

In this 12-month longitudinal study, motor and several non-motor symptoms improved in PwP; however, self-perceived stigma was largely stable. Only a small subset showed reduced stigma, and they also reported greater gains in perceived social support and reductions in anxiety. These results support adding targeted psychosocial approaches to routine PD care to address stigma and strengthen social support. Multidisciplinary models that include mental health services and community-based programs may be key to lowering self-perceived stigma and improving quality of life. Future studies should track

longer-term stigma trajectories and test structured, stigma-focused interventions. Outcomes from such interventions could be measured with dedicated tools, for example, a recently validated 18-item PDStigmaQuest now offers a comprehensive way to quantify multiple dimensions of stigma (felt stigma, hiding behavior, and enacted stigma) in PD.[17]

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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

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REVIEW ARTICLE

Dysphagia after stroke: a literature review

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Abstract

Post-stroke dysphagia (PSD) is a frequent condition and affects 80% of stroke patients. It increases the risk of malnutrition, pneumonia, and reduced quality of life. Its main risk factors include brainstem infarcts, a high NIHSS score, advanced age, hypertension, and diabetes. Pathophysiology involves both sensory and motor dysfunction with reduced spontaneous swallowing and disruption in the swallowing neural network. Early diagnosis is essential, through videofluoroscopy or fiberoptic endoscopic evaluation. Treatment combines rehabilitation, behavioral strategies, neurostimulation, and acupuncture being an alternative of treatment. Complications include malnutrition, pneumonia, and worsening quality of life. PSD worsens prognosis and requires a multidisciplinary approach to management. Despite advancements, more robust studies are needed to optimize treatment and improve clinical outcomes.

Keywords: *Dysphagia. Swallowing. Stroke. Pneumonia. Malnutrition.*

Disfagia posterior a la enfermedad vascular cerebral: una revisión de la literatura

Resumen

La disfagia posterior a un infarto cerebral (PSD) es una condición frecuente y afecta hasta el 80% de los pacientes con stroke. Incrementa el riesgo de desnutrición, neumonía y deterioro en la calidad de vida. Sus principales factores de riesgo incluyen infarto del tronco encefálico, puntuaciones altas en la escala NIHSS, edad avanzada, hipertensión y diabetes. La fisiopatología implica disfunción sensorial y motora, con reducción de la deglución espontánea y alteración en la red neuronal de la deglución. El diagnóstico temprano es esencial, mediante videofluoroscopia o evaluación endoscópica. El tratamiento combina rehabilitación de la deglución, estrategias conductuales, neuroestimulación y alternativas como acupuntura. Las complicaciones incluyen desnutrición, neumonía y peor calidad de vida. La PSD empeora el pronóstico y requiere un enfoque multidisciplinario para su manejo. Pese a los avances, se necesitan estudios más robustos para optimizar el tratamiento y mejorar los resultados clínicos.

Palabras clave: *Disfagia. Deglución. Accidente cerebrovascular. Neumonía. Desnutrición.*

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Introduction

Dysphagia refers to a swallowing disorder where food or liquid takes longer than normal to move from mouth to stomach. It may be acute, chronic, intermittent, or persistent and can stem from problems in the oropharyngeal phase, esophageal phase, or both phases of swallowing[1,2].

Dysphagia, or difficulty swallowing, affects approximately 1 in 25 adults in the general population, and its incidence and prevalence rise markedly with advancing age. Among individuals > 50 years, prevalence estimates range from 5.5% to 8%, with substantially higher rates observed in hospitalized patients and nursing home residents, particularly those over 75. Several factors contribute to this age-related increase, including muscle atrophy, chronic cardiovascular and systemic diseases, and the accumulation of neurological conditions[3,4].

Oropharyngeal dysphagia is especially common in older adults because of its strong association with neurologic disorders such as stroke, Parkinson's disease, and dementia[4]. Despite its frequency and clinical relevance, dysphagia is often underreported by patients, which leads to delayed recognition and management. This underdiagnosis is particularly concerning in older adults, who are already at heightened risk, and contributes to worse clinical outcomes, including malnutrition, pneumonia, increased mortality, and prolonged hospital stays[5,6].

Post-stroke dysphagia (PSD) prevalence varies based on diagnostic criteria, timing, assessment methods, and stroke characteristics. Studies report prevalence rates between 29% and 81% of cases[6,7], though these figures vary according to specific diagnostic methods and swallowing tests employed[8].

Understanding risk factors, diagnostic approaches, and treatment options for PSD is crucial, as they significantly impact patients' symptoms, functionality, and life quality[9]. This review examines the literature on risk factors, predictors, diagnostic methods, complications, and treatments of PSD.

Methodology

To perform this narrative review, a structured literature search was conducted to identify meta-analyses, clinical trials, cohort studies, multicenter studies, and preclinical studies that provide recent evidence on epidemiology, pathophysiology, diagnosis, and treatment of PSD. The search was performed in PubMed, Scopus, and Web of Science, using combinations of the keywords "dysphagia post-stroke OR PSD OR dysphagia after stroke" AND "risk factors", "pathophysiology", "diagnosis", "treatment", "outcomes", and "prognosis" from January to May 2025. Given the exploratory nature of this literature review, no strict exclusion criteria were applied, allowing the inclusion of all potentially relevant studies that contributed to a comprehensive and updated overview of the current scientific knowledge on PSD. Nevertheless, priority was given to the inclusion of meta-analyses, systematic reviews, randomized controlled trials, cohort studies, and multicenter research. No language restrictions were applied.

Epidemiology

Dysphagia is a prevalent condition with substantial impact across age groups. Population-based data from high-income countries indicate a prevalence of 10-20% in adults and up to 16% in the United States. Among individuals > 65 years, prevalence ranges from 13% to nearly 40%, with higher rates reported in hospitalized and neurologically impaired populations. In low- and middle-income regions, including Latin America, epidemiological data remain limited, and the available literature consistently highlights the absence of high-quality population-based prevalence data[10].

PSD constitutes one of the most frequent complications after stroke, with a global pooled prevalence of 46.6%. Marked regional variability has been reported, with the highest estimates in Oceania (64.1%) and South America (57.5%), followed by Europe (45.8%) and North America (44.3%). PSD is more frequent in women (46.2%) than men (42%) and occurs more often in individuals with previous stroke (49.9%) than in first-ever stroke (45.1%)[11]. In low- and middle-income settings, the growing stroke burden and limited access to specialized dysphagia assessment further amplify the clinical impact of PSD.

By stroke type, prevalence is 43.6% in ischemic stroke and 58.8% in hemorrhagic stroke. Gender distribution shows 42% prevalence in men and 46.2% in women. When considering stroke frequency, prevalence reaches 45.1% in 1st-time strokes and 49.9% in patients with previous strokes. Prevalence also varies by affected brain region, 64.6% in total anterior circulation infarction, 36.2% in partial anterior circulation infarction, 42.4% in posterior circulation infarction, and 44.7% in lacunar infarction[11].

Risk factors

PSD arises from a combination of pre-existing patient-related factors and risk factors directly attributable to the neuroanatomical characteristics of the stroke. Pre-existing clinical factors include advanced age (SMD 0.42), low body mass index (OR 1.28), hypertension (OR 1.96), diabetes mellitus (OR 1.83), atrial fibrillation, a history of stroke or transient ischemic attack TIA (OR 1.51 and OR 0.70, respectively), and severe cognitive impairment (OR 1.02) linked to delayed PSD recovery[12]. Reduced daily activity scores (OR 1.70) also represent a baseline vulnerability independent of lesion site. In contrast, neuroanatomical factors derive directly from the location and extent of the cerebral injury. Brainstem infarction carries the highest risk (OR 5.06), followed by bilateral hemispheric involvement (OR 3.10), both of which disrupt the central swallowing network and impair pharyngeal and laryngeal motor control[11,13]. High NIHSS scores (OR 3.47) reflect greater neurological burden and often indicate more extensive lesions that may involve multiple cortical and subcortical regions essential for swallowing control[11,14].

Protective predictors, such as early intervention (OR 0.74) and an mRS score of 0 at stroke onset (OR 0.58)[13], further underscore the importance of distinguishing baseline susceptibility from lesion-specific mechanisms when evaluating dysphagia risk.

Pathophysiology

Swallowing is a complex process requiring precise coordination of motor movements, including controlled tongue movement, pharyngeal muscle contraction, airway closure, and upper esophageal sphincter opening. Rather than functioning as a simple brainstem reflex as traditionally believed, swallowing reflects a patterned response that emerges from the interaction of sensory input and centrally organized motor programs[15].

Cortical and subcortical regions form an integrated neural network that supports the initiation and modulation of swallowing. Neuroimaging and lesion-mapping studies consistently identify the involvement of primary motor and sensory cortices, supplementary motor area, premotor cortex, anterior cingulate cortex, insula, and opercular regions during swallowing[16]. These areas initiate voluntary oral movements, process afferent input from the oropharynx, and provide essential modulatory signals to brainstem swallowing centers[16,17]. Lesions affecting the precentral and post-central gyri, insula, supramarginal gyrus, or superior temporal regions are associated with delayed swallow initiation, impaired laryngeal elevation, pharyngeal residue, and increased aspiration risk, underscoring the importance of these cortical sites for sensorimotor integration and airway protection[16].

Subcortical structures also participate critically in swallowing control, with the basal ganglia and thalamus modulating the timing, sequencing, and precision of the swallowing motor pattern through the cortico-basal ganglia-thalamo-cortical loop[17]. Lesions in the basal ganglia, corona radiata, internal capsule, and periventricular white matter correlate with more severe dysphagia, prolonged pharyngeal transit, impaired laryngeal vestibule closure, and persistent aspiration risk, highlighting the essential role of subcortical pathways in transmitting cortical commands to the brainstem and maintaining coordinated and safe swallowing[16,17].

PSD involves sensory impairment affecting both central and peripheral mechanisms. Pharyngeal hypoesthesia delays or inhibits the activation of swallowing response, leading to dysphagia. After stroke, patients exhibit a reduced frequency of spontaneous swallowing, possibly due to disrupted sensory input to swallowing centers. Studies indicate that peripheral sensory stimulation enhances motor cortex excitability, reinforcing the connection between sensory and motor systems. Moreover, decreased swallowing frequency correlates with the degeneration of sensory nerve endings that release substance P in saliva. Studies show that increasing substance P levels through pharmacological stimuli, such as capsaicin, improves swallowing function[18,19]. These findings highlight the critical role of both central and peripheral sensory impairments in dysphagia pathophysiology.

Traditional understanding held that dysphagia related to involvement of supratentorial structures required bilateral lesions. However, current evidence demonstrates that unilateral lesions outside the brainstem are sufficient to produce dysphagia, indicating that swallowing impairment arises from disruption of specific supratentorial and subcortical pathways rather than from bilateral hemispheric involvement alone[20]. Nonetheless, bilateral lesions remain associated with more severe dysphagia, poorer functional outcomes, and slower recovery trajectories[21].

Neuroplasticity

PSD is associated with the disruption of functional connectivity in the swallowing network. Swallowing has bilateral representation, and contralesional areas play

a crucial compensatory role in recovery through neuroplasticity. Studies show that after a stroke motor and sensory activity in contralesional hemisphere initially decreases but increases during the recovery phase. tDCS studies have confirmed recruitment of contralesional somatosensory areas. White matter analysis reveals that a larger volume of contralesional corticobulbar tract correlates with better swallowing function, highlighting the importance of contralesional neuroplasticity in PSD rehabilitation[15,22].

Diagnosis and dysphagia assessment

Diagnostic screening for PSD should be conducted as early as possible, given its crucial role in reducing the risk of pneumonia and mortality during stroke acute phase[7,23]. Several diagnostic methods and tools are available to assess dysphagia severity. For better understanding, they can be classified into imaging evaluation methods, instrumental assessment, clinical tests, and questionnaires.

Imaging and instrumental assessment

Imaging evaluations include videofluoroscopic swallowing study (VFSS), while instrumental assessment includes fiberoptic endoscopic evaluation of swallowing (FEES). Both are considered conventional methods for dysphagia diagnosis[24].

Clinical tests

Clinical tests are bedside assessments performed without specialized equipment. These tests help identify signs of dysphagia and aspiration risk by observing swallowing, testing cough reflexes, and assessing responses to different bolus volumes and consistencies[25].

Some clinical tests are cervical auscultation, clinical swallowing examination, volume- viscosity swallowing test, water swallowing test, standardized swallowing screen (SSA), Gugging swallowing screen (GUSS), Toronto Bedside Swallowing Screening Test (TOR-BSST), Royal Brisbane Women's Hospital Dysphagia Screening Tool, Mann Assessment of Swallowing Ability (MASA), Saliva swallowing test (SST), peak cough flow measurement, swallowing provocation test and cough reflex test[24-26]. Table 1 summarizes characteristics of imaging and instrumental assessment methods, as well as clinical tests.

Questionnaires and scales

Questionnaires and scales include the functional oral intake scale (FOIS), functional dysphagia scale, dysphagia severity rating scale, repeated Saliva swallowing test (RSST), Penetration-Aspiration Scale (PAS), and swallowing quality of life questionnaire (SWAL-QoL)[24,25,27]. Table 2 provides a tools summary.

In accordance with current European stroke organization/European society for swallowing disorders recommendations, we favor an assessment pathway that integrates early bedside screening and instrumental confirmation when needed. Among bedside tools, the GUSS and the Yale Swallow Protocol provide a strong balance of high sensitivity and feasibility for routine use in acute stroke units. For instrumental evaluation, we consider VFSS the reference method, with FEES as a complementary option when repeated assessments or avoidance of radiation are required. Overall, our preferred approach is to conduct early screening with a validated high-sensitivity test, followed by VFSS and/or FEES in patients with suspected dysphagia.

Neuroimaging

Magnetic resonance imaging (MRI) using structural and functional imaging methods is particularly valuable for the diagnosis of ischemic stroke. In addition, it allows for the identification of factors that predict subsequent alterations such as dysphagia, dysarthria, and aphasia[28].

MRI studies using activation likelihood estimation (ALE) in PSD patients have revealed structural and functional changes across multiple brain regions, including the inferior parietal gyrus, left frontal lobe, insula, internal capsule radiata, external capsule, superior longitudinal fasciculus, thalamus, primary and supplementary motor areas, and basal ganglia (caudate and lenticular nuclei)[29].

Oral phase PSD occurs more frequently when lesions are present in the inferior frontal lobe, precentral and post-central gyri, anterior cingulate gyrus, caudate nucleus, frontal lobe (including medial and inferior frontal gyri), and insula. For pharyngeal phase PSD, the risk rises with lesions in the basal ganglia, insula, inferior frontal gyrus, and parahippocampal gyrus[28,29].

Several findings are linked to increased PSD risk: pontine lesions (RR 3.7), medial medullary lesions (RR 6.9), and lateral medullary lesions (RR 9.6)[28]. Studies have identified both structural lesions and functional

Table 1. Summary of some diagnostic methods for dysphagia

Method	Description	Sensitivity and specificity (%)
FEES[18]	This diagnostic method identifies delayed swallowing initiation, pharyngeal residue and aspiration. The procedure involves inserting a flexible endoscope through the nasal cavity to directly observe pharyngeal events in real time. It offers two key advantages: patients are not exposed to radiation and the examination can be performed conveniently at the bedside.	Se: 37-100 Sp: 65-87
VFSS[18]	This is considered the diagnostic standard for evaluating oropharyngeal dysphagia because it enables direct visualization of food bolus and any potential airway penetration. The procedure involves recording the patient ingesting water-soluble contrasts of varying volumes and viscosities.	Se: 29-33 Sp: 96-100
V-VST[16]	This procedure detects oropharyngeal dysphagia by administering three series of boluses (5, 10, and 20 mL) with different viscosities, such as nectar, liquid and pudding. Testing begins with the smallest nectar bolus and gradually increases in volume until the patient shows signs of swallowing difficulty.	Se: 83.3-96.6 Sp: 71.4-72.6
WST[16]	The test requires patients to drink a set volume of water (50 or 90 mL). A positive result occurs if aspiration signs develop during or after the procedure, including coughing, voice changes or stridor.	Se: 72 Sp: 67
Yale Swallow Protocol[16]	A standardized protocol for assessing dysphagia and aspiration risk. The method verifies safe swallowing criteria, evaluates oral and pharyngeal function, and includes a water swallow test. Patients must drink 3 ounces (90 mL) of water continuously without stopping.	Se: 95.4 Sp: 66.9
RBWH DST[16]	A nurse-administered swallowing screening tool consisting of three steps: an initial two-phase screening, a water swallowing test if needed, and the development of a swallowing management plan.	Se: 93 Sp: 96
SSA[16]	It is a standardized test used to identify swallowing difficulties and evaluate aspiration risk. It consists of an evaluation of oral function, swallowing, and the presence of aspiration signs, such as coughing or changes in voice. It is a useful tool for detecting dysphagia in early stages and appropriate treatment.	Se: 94.5 Sp: 65
TOR-BSST[16]	A clinical screening tool that detects early signs of dysphagia risk in patients. The evaluation proceeds through several phases to assess swallowing function and determine whether the patient requires more detailed testing.	Se: 80 Sp: 68
GUSS[16]	A clinical test that evaluates swallowing disorders and aspiration risk in early stages. The assessment includes a preliminary investigation followed by a direct swallowing test using various food textures.	Se: 89.5 Sp: 87.5
SST[16]	A tool that valuates swallowing safety and effectiveness with liquids. The patient swallows a measured amount of liquid (3-5 mL) as the evaluator monitors clinical signs.	Se: 28 Sp: 76

FEES: fiberoptic endoscopic evaluation of swallowing; VFSS: videofluoroscopic swallowing study; V-VST: volume-viscosity swallowing test; WST: water swallowing test; RBWH: Royal Brisbane Women's Hospital Dysphagia Screening Tool; SSA: standardized swallowing assessment; TOR-BSST: Toronto Bedside Swallowing Screening Test; GUSS: gugging swallowing screen; SST: saliva swallowing test; Se: sensitivity; Sp: specificity.

changes in the sensorimotor cortex, insula, cerebellum, cingulate gyrus, thalamus, basal ganglia, and white matter connections. Further analysis using ALE has shown heightened risk associated with lesions in the right lenticular nucleus and right thalamus, as well as functional abnormalities in the left thalamus[29,30].

Treatment

Due to the lack of specific pharmacological treatments for swallowing disorders, healthcare providers have implemented various non-pharmacological interventions, including behavioral approaches, neurostimulation, swallowing therapies, and acupuncture.

Compensatory maneuvers

Compensatory maneuvers in PSD aim to improve airway protection and bolus transit by modifying the characteristics of swallowing without altering the underlying physiology. These strategies include adjusting bolus volume and speed through fractionated or paced swallowing, using measured spoons to regulate intake, and applying supraglottic, super supraglottic, and effortful swallow techniques to enhance laryngeal closure. Modifying bolus consistency, such as thickening liquids or altering solid textures, is also routinely implemented to reduce the risk of penetration and aspiration[31].

Table 2. Summary of dysphagia assessment methods used in patients with PSD

Tool or method	Description
PAS[17]	Scoring system that evaluates eight domains and detects both penetration and severity of aspiration during videofluoroscopic swallowing studies. It is divided into eight levels: level 1 indicates that material does not enter the airway, levels 2 through 5 indicate different degrees of penetration, and levels 6 through 8 represent different levels of aspiration severity.
FOIS[17]	Seven-level scale that evaluates oral intake function: level 1 indicates nothing by mouth, levels 2 and 3 indicate enteral feeding dependency, and levels 4 through 7 correspond to oral feeding.
FDS[17]	This instrument assesses dysphagia and aspiration risk while evaluating a patient's ability to safely swallow liquids and foods of varying consistencies. The assessment consists of two phases: an indirect phase to determine if the patient can safely undergo swallowing tests and a direct phase to evaluate swallowing function.
RSST[17]	A test that assesses swallowing function and dysphagia risk by measuring a person's ability to swallow saliva repeatedly within a specific timeframe. This can reveal signs of muscle weakness or swallowing disorders.
DSRS[17]	Scale that classifies dysphagia severity. It comprises 7 levels, where level 1 indicates normal swallowing, levels 3-6 indicate progressive severity, and level 7 indicates total aspiration.
SWAL-QoL[17,19]	A self-administered 44-item questionnaire that assesses quality of life across 11 domains in patients with oropharyngeal dysphagia: burden, eating duration, appetite, symptom frequency, food selection, communication, fears, mental health, social aspects, fatigue and sleep.

PAS: penetration aspiration scale; FOIS: functional oral intake scale; FDS: functional dysphagia scale; RSST: repetitive saliva swallowing test; DSRS: dysphagia severity rating scale; SWAL-QoL: swallowing quality of life questionnaire.

Postural and behavioral maneuvers

Postural maneuvers involve adjusting head or body position to redirect bolus flow and improve swallowing safety. Commonly used techniques include the chin tuck maneuver, head rotation toward the weaker side, head tilt toward the stronger side, neck extension, and strategic repositioning of the body during feeding. Behavioral and environmental strategies complement these adjustments by optimizing the feeding context. These include caregiver training to support safe feeding practices, promoting self-feeding in appropriate patients, managing fatigue during meals, adapting utensils when needed, and minimizing distractions to facilitate concentration and coordination. These interventions may be combined with sensory stimulation techniques, such as tactile, thermal, or chemical stimuli, to enhance the initiation and coordination of swallowing[15,32,33].

Swallowing maneuvers

Therapeutic swallowing maneuvers focus on strengthening the musculature involved in deglutition and improving the physiological components of swallowing. These interventions encompass lingual strengthening, resistance-based exercises, the Mendelsohn maneuver, the Shaker exercise, and other forms of suprahyoid muscle training[32]. Chin tuck against resistance (CTAR), a more recent technique, has demonstrated meaningful clinical benefits in PSD rehabilitation. A meta-analysis showed that CTAR improved swallowing safety and functional oral intake compared with no exercise and was more effective than the Shaker exercise for enhancing airway protection. Beyond its physiological effects, CTAR was also associated with better patient-reported psychological outcomes. Prior studies evaluating oropharyngeal muscle strengthening exercises have similarly shown improvements in swallowing efficiency, oral intake levels, and hyoid movement, along with a reduction in complications such as pneumonia across different types of therapeutic maneuvers[32-34]. Together, these findings indicate that structured strengthening programs, including CTAR, play an important role in restoring swallowing function in PSD.

Neurostimulation

Neurostimulation in PSD promotes cortical reorganization and enhances synaptic efficacy, accelerating the recovery process from cerebral infarction[34]. Among the most used neurostimulation methods for treating patients with PSD are transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), superficial neuromuscular electrical stimulation (sNMES), and pharyngeal cavity electrical stimulation (PCES)[35].

Therapies with TMS, tDCS, sNMES, and PCES have shown greater effectiveness in treating and improving dysphagia (rTMS: SMDZ 1.06, 95% confidence interval [CI] 0.64-1.47, tDCS SMDZ 0.61, 95% CI 0.14-1.08, sNMES: SMDZ 0.76, 95% CI 0.26-1.26) compared to placebo. rTMS appears to be the most effective therapy among the different modalities[35,36].

Neuromuscular electrical stimulation

NMES is a peripheral stimulation technique that uses transcutaneous electrical current to generate contractions of the suprahyoid muscles to elevate the hyoid and larynx (geniohyoid, mylohyoid, and anterior belly of the digastric muscle), as well as the infrahyoid muscles to depress the hyoid and larynx (omohyoid, sternohyoid, and sternothyroid)[35]. It can improve swallowing function by stimulating peripheral nerves to trigger contraction of the swallowing muscles, promote motor cortex repair, and enhance motor relearning capacity[37].

NMES shows effectiveness when combined with conventional therapies, including thermal and traditional stimulation, McNeill therapy, and other rehabilitation methods. In combination with these therapies, it has been associated with significant improvements in FOIS scores (SMD 0.48, $p < 0.0001$), PAS scores (SMD 0.48, 95% CI 1.01-0.10), and SWAL-QoL (SMD 0.57, 95% CI 0.00-1.14, $p = 0.05$)[38].

Pharyngeal cavity electrical stimulation

PCES is a peripheral neurostimulation technique that involves a catheter, which can be placed in the pharynx either transnasally or transorally to transmit a small electrical current of 5 Hz through the pharyngeal mucosa passively. Electrical stimulation increases sensitivity and, through indirect pathways, enhances cortical modulation of swallowing by promoting cortical reorganization[39].

Effective PCES are applied at a frequency of 5 Hz for 10 min/day over three consecutive days. However, studies have yet to demonstrate its impact on swallowing improvement or any significant association with a reduction in aspiration between 2 weeks and 3 months after treatment[35]. A meta-analysis conducted by Liu et al.[40] compared the outcomes of PCES, routine rehabilitation, and a control group in patients with PSD. The findings indicate that PCES use is significantly associated with improved extubation success rates of the nasogastric tube used for enteral feeding (RR 2.88), compared to the control group.

Transcranial direct current stimulation

tDCS is a technique that modulates brain activity by altering neuronal membrane potential. Two electrodes placed on the scalp deliver constant low-intensity stimulation (1-2 mA). The anode is positioned over brain areas targeted for stimulation, while the cathode is placed over areas requiring suppression[39]. This non-invasive technique produces therapeutic effects through two mechanisms: the anode depolarizes the resting membrane potential to increase neuronal excitability, while the cathode hyperpolarizes it to reduce neuronal excitability[35].

The advantages of this technique include its non-invasiveness, ease of equipment operation, minimal side effects, and low cost. However, tDCS efficacy heavily depends on stimulation parameters and frequency. The use of anodal tDCS for 20 min at doses of 1.2, 1.4, 1.5, 1.6, or 2 mA and for 30 min at 2 mA significantly improves PSD, with the optimal dose being 1.4 mA for 20 min (SMD −0.71, 95% CI −1.05 to −0.36)[41].

Transcranial magnetic stimulation

TMS is a neuromodulation technique whose purpose is to regulate neuronal membrane potential using electromagnetic energy pulses through a copper coil placed on the scalp[42]. It consists of administering frequencies of 3-5 Hz over the cortical swallowing centers to cause neuronal excitation, and conversely, neuronal suppression occurs with low frequencies (1 Hz). The number of pulses per session varies from 300 to 1,800 pulses/session with an average of 5-10 sessions, although up to 20 sessions can be given[39].

Multiple studies and meta-analyses have investigated TMS effects in PSD patients. A meta-analysis conducted by Sun et al.[42] found that 3 Hz stimulation yielded superior PAS scale scores compared to 5 Hz and 10 Hz frequencies. The study also revealed that applying stimulation to the stroke-affected region produced better PAS score improvements than stimulating healthy areas or using bilateral stimulation.

A meta-analysis conducted by Hsiao et al.[43] found significant improvements in SSA scores following high-frequency rTMS applied to the cortex contralateral to the lesion with immediate results (SMD = −0.61, $p = 0.02$) and sustained effects at 4 weeks post-treatment (SMD = −0.74, $p = 0.006$). However, it has been suggested that bilateral stimulation might offer greater overall swallowing benefits compared to unilateral stimulation, whether ipsilesional or contralesional[44].

In addition, a meta-analysis conducted by Tan et al.[45] confirmed that rTMS significantly improves swallowing function after intervention (Z = –2.71, p = 0.01), reinforcing its effectiveness in PSD treatment.

Acupuncture

Acupuncture is a treatment modality used in the rehabilitation of patients with ischemic stroke. It involves inserting needles into specific acupuncture points on the body surface with stimulation through manual rotation or electrical pulses[46].

Evidence on the use of acupuncture is heterogeneous across different randomized clinical trials and meta-analyses. However, improvement in swallowing has been demonstrated in patients with PSD compared to placebo[47]. This therapeutic benefit is explained by the belief that acupuncture promotes neuroplasticity by stimulating the proliferation, migration, and differentiation of neural stem cells, which contributes to the improvement of neurological deficits, such as PSD[48]. In a study, improvement was observed in VFSS scores in patients treated with 10 weekly sessions (WMD 1.23, 95% CI 2.29-4.07), compared to those who received 5 or 6 weekly sessions (WMD 0.80, 95% CI 0.55-1.05)[49].

The use of neck acupuncture combined with rehabilitation training led to greater improvement in patients with PSD (OR 4.25, CI 95% 2.94-6.15), higher scores in VFSS studies (WMP 1.33 CI 95% 1.09-1.58, z = 10.82, p < 0.001) and lower scores in SSA (WMD –2.57, CI 95% –3.51 to –1.62, z = 5.33, p < 0.001). Among the adverse effects, 18% reported bleeding, 12.5% hematoma, and 20% needle pain[50].

For dysphagia due to pseudobulbar palsy, acupuncture has shown improvement in PSD (RR 1.51, 95% CI 1.30-1.75), both when applied alone or combined with rehabilitation (RR 1.38, 95% CI 1.08-1.76), compared to conventional rehabilitation. Regarding adverse effects, only two clinical trials reported mild pain during initial treatment with no manifestations during follow-up[51].

Through evaluation and therapeutic tools, we propose an algorithm for the diagnosis and management of patients with PSD, which is presented in figure 1.

Nutritional management

Early enteral tube feeding is an essential component of nutritional support in patients with severe PSD who cannot safely meet caloric requirements through oral intake[52]. Evidence from the FOOD Trial indicates that initiating tube feeding during the initial 72 h, may offer a modest reduction in early mortality, although it does not significantly alter the combined endpoint of death or severe disability at 6 months. Nasogastric feeding is considered the preferred short-term method because it is minimally invasive, easy to place, and suitable for patients in whom swallowing recovery is expected during the first 2-4 weeks. During this period, caloric intake should be closely monitored to ensure adequate nutritional support while reassessing swallowing safety[53].

When dysphagia persists, and the need for enteral nutrition extends beyond 4 weeks, percutaneous endoscopic gastrostomy (PEG) should be considered as the preferred long-term strategy[54]. PEG placement is generally reserved for individuals with sustained swallowing impairment and an anticipated prolonged need for enteral support. PEG offers advantages such as improved feeding stability and reduced risk of tube displacement compared with nasogastric feeding, but it is also associated with higher medium- and long-term mortality, reflecting the severity and complexity of the underlying neurological condition[55]. For this reason, the decision to place a PEG tube should incorporate the expected duration of dysphagia, overall prognosis, functional status, and patient-centered goals of care.

Liquid thickening is a technique that involves adding a thickening agent to liquids to increase their viscosity and reduce bolus speed to prevent aspiration. It has been reported that 78% of speech therapists and up to 97% of those who work with stroke patients use this intervention[56]. In addition, between 20% and 70% of patients with PSD modify food consistency or resort to permanent enteral or parenteral nutrition[57,58]. Due to limited evidence on liquid thickening, some clinical practice guidelines do not recommend it. However, others suggest performing a nutritional assessment to determine the need for liquid thickening, food consistency modification, or the use of parenteral or tube feeding in patients with suspected aspiration, considering each case individually[56].

PSD-related complications

Malnutrition

Malnutrition is a frequent complication in stroke patients, with its incidence increasing significantly in those with PSD. It is observed in 19-72% of patients, and in 30% of cases it persists during follow-up. It is associated with unfavorable functional prognosis (mRS ≥ 3), higher incidence of complications during hospitalization,

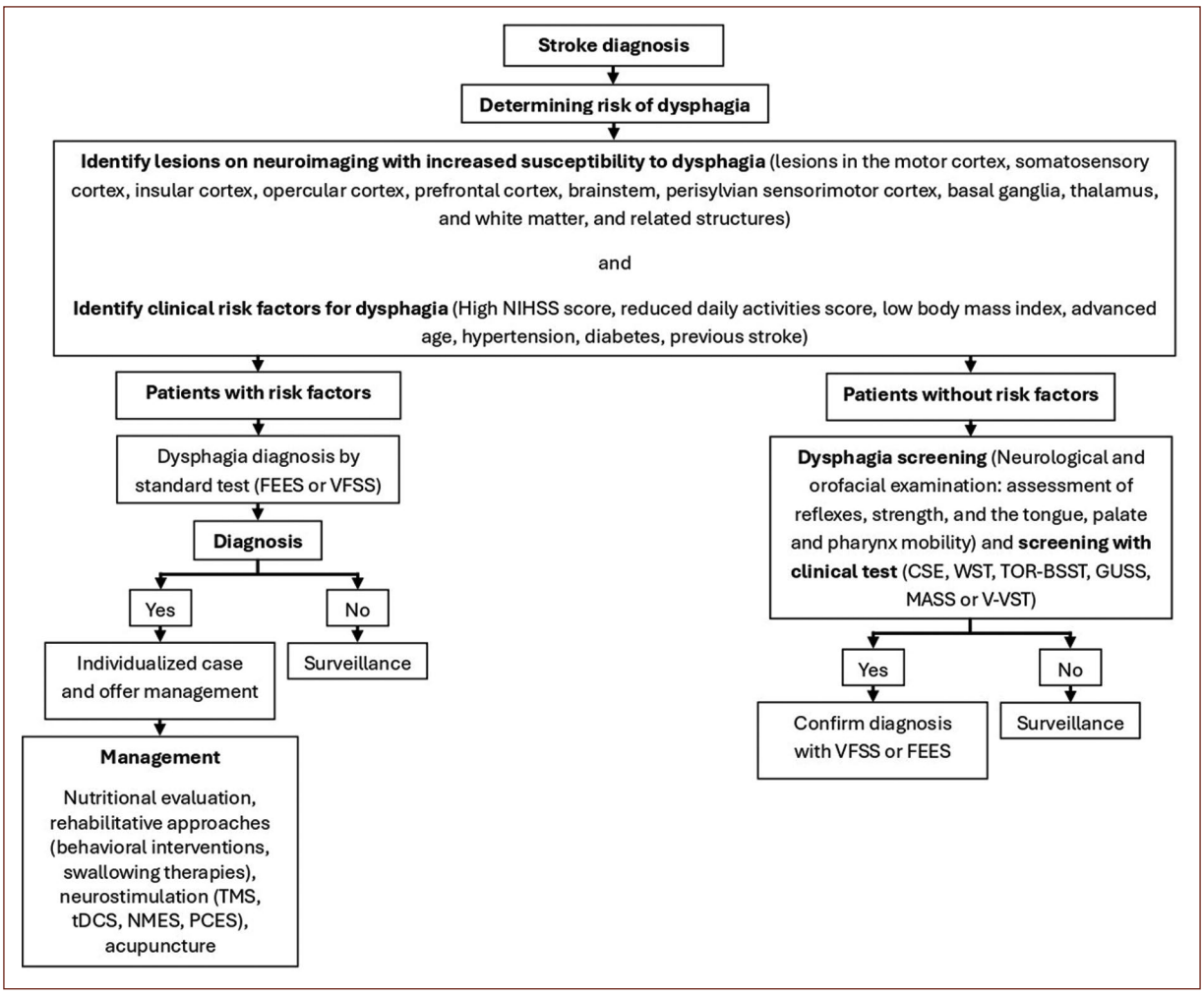

Figure 1. Diagnostic and management algorithm for patients with post-stroke dysphagia.

increased mortality, longer hospital stays, and elevated hospitalization costs[59].

Dysphagia increases the risk of malnutrition (OR 2.42) compared to patients with intact swallowing and increases its frequency during the rehabilitation phase (OR 2.44)[60]. Furthermore, in patients with dysphagia and malnutrition, greater difficulty returning to a normal diet has been described, which worsens their nutritional status and delays their overall recovery[6].

Pneumonia

PSD significantly increases the risk of pneumonia (RR 8.4). In patients with PSD, aspiration pneumonia develops in 20-47% of cases, leading to extended hospital stays, poor clinical outcomes, and a threefold higher 30-day mortality rate[61]. Early detection of aspiration risk through dysphagia screening significantly reduces pneumonia occurrence (OR 0.60, 95% CI 0.42-0.84, p = 0.003, I^2 = 66%)[62]. Among screening tools, bedside aspiration tests, GUSS, and TOR-BSST have demonstrated the highest accuracy in identifying aspiration risk[63].

Prognosis

The prognosis of PSD varies according to baseline functional status and specific clinical predictors. A meta-analysis identified early intervention (OR 0.75) and a modified Rankin Scale score of 0 before stroke onset (OR 0.58) as protective factors for better swallowing outcomes, while older age (OR 1.75), severity of stroke expressed through higher NIHSS scores (OR 3.06), malnutrition (OR 1.36), severe dysphagia on admission (OR 1.16), reduced level of consciousness (OR 1.03), aspiration (OR 7.64), brainstem injury (OR

Table 3. Summary of key findings from the review

Risk factors	Brainstem infarction, bilateral hemispheric infarction, higher NIHSS scores, reduced scores on daily activity scales, low body mass index, advanced age, hypertension, diabetes, prior cerebral infarction, history of TIA, and atrial fibrillation.
Diagnosis	Early diagnosis through standard methods such as VFSS and FEES, or alternative methods including V-VST, WST, SSA, TOR-BSST, GUSS, SST, Yale Swallow Protocol, and RBWH.
Treatment	Behavioral interventions Swallowing therapy: structured rehabilitation exercises for improving swallowing function Nutritional interventions: nasogastric tube feeding, percutaneous gastrostomy, food consistency modification, and liquid thickening Neurostimulation: neuromuscular electrical stimulation, pharyngeal cavity electrical stimulation, transcranial direct current stimulation, and transcranial magnetic stimulation Acupuncture
Complications	Malnutrition: nutritional assessment to evaluate nutritional status, need for food consistency modification, liquid thickening, or tube feeding. Aspiration pneumonia: perform early assessment of aspiration risk and dysphagia to prevent complications. Deterioration in quality of life: provide swallowing rehabilitation and individualized treatments to restore swallowing function.

FEES: fiberoptic endoscopic evaluation of swallowing; VFSS: videofluoroscopic swallowing study; V-VST: volume-viscosity swallowing test; WST: water swallowing test; RBWH: Royal Brisbane Women's Hospital Dysphagia Screening Tool; SSA: standardized swallowing assessment; TOR-BSST: Toronto Bedside Swallowing Screening Test; GUSS: gugging swallowing screen; SST: saliva swallowing test.

4.82), and bihemispheric injury (OR 3.0) were associated with poorer prognosis[59].

In addition, a systematic review reported that age, airway compromise detected on instrumental assessment, dysphagia severity, bilateral lesions, and overall stroke severity were significant predictors of persistent dysphagia and unfavorable recovery in multiple logistic regression analyses[9].

Impairment in quality of life

Quality of life in PSD patients has been assessed using two main instruments: the SWAL-QoL and the dysphagia handicap index. SWAL-QoL studies showed that PSD patients experience significantly lower quality of life compared to those without PSD. Studies found a negative correlation between dysphagia severity and quality of life, as severity increases, quality of life decreases, particularly in the areas of burden ($r = -0.392$, $p = 0.001$), social functioning ($r = -0.370$, $p = 0.001$), mental health ($r = -0.362$, $p = 0.014$), fatigue ($r = -0.401$, $p = 0.041$), food choice and sleep. Importantly, patients who underwent swallowing rehabilitation experienced improvements in their quality of life[27]. Table 3 summarizes the key findings in this review.

Conclusion

PSD is a prevalent condition that worsens prognosis, increases mortality, and causes additional complications. Lesions in multiple brain regions cause PSD, particularly in the cerebral and premotor cortices. Early detection enables personalized treatments, which include behavioral interventions, neurostimulation, swallowing therapies, and alternative approaches like acupuncture. Despite considerable evidence on PSD, many studies suffer from methodological limitations and similar designs, limiting comprehensive analysis of various aspects and treatment outcomes. Therefore, studies with more robust methodologies are needed to enable thorough meta-analysis evaluation.

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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. 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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REVIEW ARTICLE

Latent inhibition: learning something new from the familiar

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Abstract

Latent inhibition (LI) is defined as the decrease in associative learning when one or more stimuli have been previously experienced without apparent consequences. This narrative review aims to compile the scientific evidence that has contributed to a growing understanding of the LI phenomenon. We begin with a brief chronological overview of how hypotheses and evidence regarding LI have emerged over the decades. We then describe LI theories from the perspective of impaired association due to interruption or discontinuity in acquisition, as well as impaired retrieval stemming from execution deficits during memory recall. In this review, we will present evidence that supports LI as a latent learning model, primarily elucidating how learning is updated through subsequent experiences. We will explain the LI of conditioned taste aversion, an experimental model used in research. Finally, we will mention LI studies that partially explain aspects of certain psychopathologies of learning. Future research on the neurobiology of LI can use these findings to elucidate the complexity of brain plasticity that underlies changes in eating and motivational behavior, including the loss of self-control through constant learning processes (pre-exposures) despite the seriously detrimental health effects.

Keywords: *Latent inhibition. Schizophrenia. Pre-exposure. Psychopathology. Gustatory aversive paradigm.*

Inhibición latente: aprendiendo algo nuevo de lo familiar

Resumen

La inhibición latente (IL) se define como la disminución del aprendizaje asociativo, cuando uno o varios de los estímulos han sido previamente experimentados sin consecuencias aparentes. En esta revisión narrativa se recopila evidencia sobre el fenómeno de la IL, iniciando con una breve reseña de las hipótesis y evidencias surgidas a lo largo del tiempo. Describimos las teorías de la IL basadas en la alteración de la asociación por interrupción o discontinuidad en la adquisición, así como por déficit en la ejecución durante la evocación de la memoria. Asimismo, resumimos evidencia que señala a la IL como un modelo de aprendizaje latente que ayuda a entender la actualización de la memoria, debida a experiencias subsecuentes. Explicaremos la IL del condicionamiento aversivo al sabor como uno de los modelos experimentales utilizados. Finalmente, mencionaremos algunos estudios de IL que explican aspectos de ciertas psicopatologías del aprendizaje que, a través de futuras investigaciones de la neurobiología del IL, pueden ayudar a dilucidar la complejidad de la plasticidad cerebral que subyace a los cambios en la conducta alimentaria y motivacional, incluida la pérdida de autocontrol a través de procesos de aprendizaje constantes (preexposiciones) a pesar de los efectos seriamente perjudiciales para la salud.

Palabras clave: *Inhibición latente. Esquizofrenia. Preexposición. Psicopatología. Paradigma aversivo gustativo.*

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Introduction

The study of LI emerged in the 1930s, rooted in Tolman's learning theory derived from his studies with mazes and rodents, leading to the postulation that "latent" (i.e., "hidden") learning occurs during these tasks. This learning can be expressed when multiple stimuli coexist during a new association that underlies a motivated or reinforced behavior.[1] However, the integration of latent learning into the formal description of LI was accidental. In 1957, Lubow, a researcher at Cornell University, studied associative learning, particularly Pavlovian conditioning, and its relationship to induced experimental neurosis. His findings led him explore a type of conditioning that is analogous to the latent learning observed in spatial discrimination in the Tolman maze. Lubow, in collaboration with Ulric Moore, designed an experiment involving goats and sheep to observe the effect of stimulus pre-exposure (PE) on a model of aversive associative learning. This experiment consisted of presenting an audiovisual stimulus (conditioned stimulus [CS]) and then an electric shock to the animals' limb (unconditioned stimulus, [US]). Leg flexion only occurred when the CS was presented, following the association of both stimuli. Unexpectedly, animals pre-exposed to an audiovisual stimulus exhibited a decrease in their ability to associate an electric shock with the CS.

Paradoxically, the main objective of the study was to find a facilitation effect from PE; however, the experimental design failed to improve learning and instead resulted in a decrease in conditioning.[2] Lubow called this phenomenon "latent inhibition." It is referred to as "latent" because learning is not evident until a later association takes place, and "inhibition" because PE to the stimulus reduces subsequent associative learning related to that same stimulus.

This work is a narrative synthesis based on a bibliographic search. It aims to provide an overview and theoretical perspective derived from scientific reports. We conducted a search on MEDLINE (PubMed) using the following subject headings: (LI) and/or (incidental) and/or (conditioned taste aversion [CTA]). Original articles and scientific review articles were selected for inclusion. Accordingly, LI is defined as a delay or decrease in learning after PE to CS, indicating a decrease in the associative strength of a stimulus that has been passively presented compared to a novel stimulus.[3]

Definition of latent inhibition (LI)

Various definitions and hypotheses exist to explain LI from behavioral, psychological, psychopathological, and pharmacological perspectives.[4-7] In clinical settings, LI has been used to elucidate the dysfunctions associated with attention deficit disorder and schizophrenia.[8] In psychology, LI has contributed to theories of attention, and in basic research, it has been utilized to study memory processes. "Latent inhibition" stems from the term "latent learning"; however, LI is not an element of learning or memory that can be distinctly identified at a given moment in observed behavior. Instead, it is a continuous process throughout the succession of learning experiences and is therefore only observable upon the conclusion of certain learning update conditions. Several neurobiological mechanisms underlie this sequence of learning processes, highlighting the significance of understanding the learning events and memory updating processes that trigger daily experiences with similar stimuli, as well as during pathological disorders that impact the accurate association of complex contexts.[9]

Outstandingly, the research of Lubow et al. marks the beginning of a new era in the study of incidental memory dynamics, focusing on associative differences for the same stimulus depending on the consequences and subsequent learning types. Over the years, research on LI has grown significantly. Recent studies have demonstrated LI in a wide range of animal species across the phylogenetic scale, from invertebrates to humans, as well as in numerous associative learning models. Evidence indicates that LI provides a cognitive and evolutionary advantage for organisms, playing an essential adaptive role in the processing of irrelevant environmental information. Furthermore, LI facilitates the processing of comparisons and adjustments to experiences, thus preventing sensory overload from familiar stimuli and favoring attention and selective association with novel and relevant stimuli. Current neurobiological knowledge of learning highlights the importance of understanding the neural mechanisms underlying the proper processing of incentive relevance in stimuli. This understanding is crucial not only for evolutionary survival but also for addressing learning impairments associated with pathologies such as schizophrenia and addiction.

LI theories

When a stimulus is presented repeatedly without being associated with relevant or quantifiable consequences, it progressively loses its associative capacity. This phenomenon may indicate a loss of "attention," rendering the stimulus "irrelevant" and delaying the learning process. Research has supported

a few theories to explain why PE to stimuli can weaken the learning process. One theory suggests that learning is affected due to an alteration in the formation of associations between stimuli (i.e., acquisition deficit). Another theory is that the retrieval/recall of associated information is altered (i.e., execution/retrieval deficit).

Theories of acquisition deficits

There are two main leading research positions, one of which includes three theories: (a) the conditioned inhibition theory,[10] (b) the habituation theory,[11] and (c) the theory of response by competence.[12] These theories postulate that CS PE causes an associative reduction that weakens the connection between CS and US, resulting in an acquisition deficit.

A second position includes (d) the theory of selective attention[13] and (e) the theory of conditioned attention,[14] which posit that PE to a familiar CS alters the acquisition of CS-US stimuli because the CS is not novel. Table 1 shows the conceptual development of the LI phenomenon, from theories of behavior and cognition to neurochemical and computational models.

Theories of memory retrieval deficits

Over time, research has shown the challenges of explaining LI through the impaired acquisition hypothesis, particularly because the variation in time interval between the acquisition and memory retrieval phases differentially changes the intensity of LI, depending on the delay between these phases. This indicates that the association between stimuli is acquired but not recalled during the memory test. The main theories supporting this argument are the Miller and Matzel theory,[15] the Bouton theory,[16] the Schmajuk-Lam-Gray mathematical model theory,[17] and the contextual differentiation theory (Table 2).[18]

The relevance of incentives: novelty versus familiarity

Current neurobiological studies examine the neural mechanisms that parallel associative learning and shape complex behaviors; for example, the degree of experience between novelty and familiarity plays an essential causal role in the strength and trajectory of associative learning. In this regard, LI studies directly impact the possibility of understanding higher-order cognitive processes that occur during complex associative learning.

It is well known that both neutral and valence stimuli exert the most significant influence on behavior when they are novel, resulting in robust learning when they are associated with positive or negative outcomes. On the other hand, the habituation process – which involves a reduction in responses to stimuli after repeated presentations – is a fundamental form of learning based on the transition from novelty to familiarity, enabling organisms to ignore irrelevant stimuli in their environment. Thus, novel stimuli can alter conditioned responses to previously learned signals associated with external cues that ensure adequate prediction. In addition, the US can become more strongly associated with novel neutral cues or CSs than with familiar cues, which can prevent or delay the associative process (i.e., LI).[3] The valence, salience, and novelty of a stimulus are characteristics that significantly influence virtually all models of associative learning, framing the complexity of how novelty affects behavior and the interactions between stimulus novelty/habituation and future learning.[19] In this context, a stimulus-related property that is gaining attention in new theories of associative learning and reinforced behaviors is motivational salience [MS]), also known as attribution of incentive relevance. MS is a cognitive process that motivates or drives an organism's behavior toward or away from a particular object or goal. In other words, it drives the "appetitive" or "aversive" response to a stimulus or event perceived as a consequence or outcome of a behavior. Thus, MS regulates the intensity, amount of time, and energy invested in the behavior that allows for the achievement of a particular goal. Thanks to memory processes, which confer a positive or negative attribute upon repetition, the motivational components of a stimulus – associated with gratification or aversion – are included or reinforced in MS.[11] A relevant context enhances the incentive associated with a stimulus so that it becomes either appetitive or aversive. However, this effect is generally less pronounced when there is previous experience with that stimulus, which has formed an incidental memory.[20] This incidental memory produces shifts in the intensity and attention paid to the stimulus, leading to alterations in its appetency, which manifest as approach or avoidance behaviors. In other words, when a stimulus is experienced under neutral incidental conditions or without clear consequences, its potential association remains latent, and when the context changes, the LI process begins. Therefore, LI studies are important for understanding higher-order cognitive processes that occur during complex associative learning.

Table 1. Conceptual development of latent inhibition

Era/Framework	Core concept	Representative advances	Disciplinary focus	References
1930s-1950s	Latent learning and associative processes	Tolman's maze studies; Lubow's goat/sheep paradigm	Behavioral psychology	1,2
1960s-1980s	Attention and conditioning	Development of selective attention theory; habituation and conditioned inhibition	Experimental psychology	3,10,13
1990s	Psychopathological application	Schizophrenia, dopamine dysfunction, antipsychotic effects on LI	Clinical neuroscience	4,6
2000s-2010s	Neurobiological and computational models	Dopaminergic-hippocampal circuits; SLG model	Systems neuroscience	5,9,11
2020s-present	Integrative neurocognitive frameworks	fMRI and optogenetic studies; LI as a biomarker for salience processing	Cognitive and translational neuroscience	7

LI: latent inhibition; SLG: Schmajuk-Lam-gray; fMRI: functional magnetic resonance imaging.

Table 2. Latent inhibition theories

Category	Theory	Main proposition	Key prediction or mechanism	Representative references
Acquisition deficit theories	Conditioned inhibition theory	Pre-exposure to the CS leads to the development of inhibitory associative strength that suppresses subsequent CS-US learning.	The CS becomes a signal for the absence of the US, delaying acquisition when conditioning begins.	10
	Habituation theory	Repeated non-reinforced presentations of the CS cause a progressive reduction in its perceptual and attentional salience.	The CS elicits reduced orienting responses and fails to capture attention during conditioning.	11
	Response-competence theory	LI arises from a general decrement in the response to repeated stimuli rather than from changes in associative strength per se.	Behavioral output, rather than learning per se, is suppressed during conditioning.	12
	Selective attention theory	Pre-exposure reduces the allocation of attention to the CS, lowering its associability with the US.	LI magnitude depends on attentional control; novel CSs gain higher associative value than familiar ones.	13
	Conditioned attention theory	Attention is itself a conditioned process; familiar CSs acquire low attentional value through pre-exposure.	Learning rate decreases for previously attended stimuli that no longer predict consequences.	14
Retrieval deficit theories	Miller and Matzel's theory	LI reflects failure in retrieval of the CS-US association rather than failure to acquire it.	Manipulations that enhance retrieval (e.g., reminder cues) should reduce LI.	15
	Bouton contextual theory	Contextual cues during pre-exposure and conditioning control retrieval of learned associations.	Changing contexts between pre-exposure and conditioning disrupts retrieval and modulates LI.	16
	SLG model	A computational model integrating attention, learning rate, and context representations to explain LI dynamics.	LI arises from predictive error-driven modulation of associability within a neural network model.	17
	Contextual differentiation theory	LI results from context-dependent retrieval competition between "irrelevant" and "relevant" associations.	Greater contextual overlap between pre-exposure and test phases enhances LI.	18

SLG: Schmajuk-Lam-Gray; LI: latent inhibition; CS: conditioned stimulus; US: unconditioned stimulus.

Experimental procedures for the study of LI

Various learning paradigms have been used in the study of LI, including classic associative (Pavlovian) and operant paradigms. In addition, experimental procedures utilize diverse variables to study LI, such as the number of PEs, duration of PE, stimulus and context specificity, and time of day. The following is a brief explanation of these variables: (1) Number of PEs: A single PE is enough to observe LI in tasks like CTA,[21] inhibitory avoidance,[22] and fear conditioning.[23] Nevertheless, a greater number of PEs is required for levering or object discrimination tasks.[24] (2) PE duration: the amount of time between PE and the presentation of the US associated with the CS. This period is crucial for the observation of LI. (3) Stimulus and context specificity: the context of PE plays a fundamental role in LI. When the PE, conditioning, and testing phases are carried out in the same context, LI is more robust. However, if changes occur in the context from the day of PE to the day of conditioning, and from conditioning to the day of recall, LI is not observed.[25] (4) Time of day: it can act as an internal cue; thus, LI can be decreased if PE and conditioning take place at different times of the day.[26]

Regarding the four previously described variables, some learning paradigms have focused on two basic phases: PE and conditioning. In PE, the CS is presented alone; subsequently, in conditioning, the original or pre-exposed CS is presented, followed by a US.[3] LI is observed as the delay in CS-US learning during the conditioning phase in the pre-exposed group. The evolution of the PE effect over several conditioning trials is an advantage that has been utilized in various works with this experimental design, such as research on CTA,[27] conditioned emotional response,[28] active avoidance,[29] eyelid conditioning,[30] and appetitive Pavlovian conditioning.[31]

LI in the CTA model

The CTA model was first described in 1955.[32] Since then, it has served as a valuable tool in various research areas, as a wide range of substances can be used as CSs with flavors that have hedonic values, from appetitive (e.g., non-caloric sweeteners like saccharin[33] to aversive (e.g., salt, coffee, alcohol, vinegar, grape, vanilla, and methadone.[34] Likewise, researchers can use harmful substances or aversive stimuli in CTA as USs, such as oral or intraperitoneal lithium chloride,[35] spinning wheels or induced body rotation, physical exercise, cobra venom, nicotine, morphine, cocaine, and radiation, among others.[36]

In 1963, McLaurin et al. provided the first LI of CTA studies, which established that PE to a flavor decreases its conditioned association (CS-US); that is, it weakens the CTA.[37] Since then, LI in CTA has been extensively and consistently studied due to the ease of replication in the laboratory and the robustness of the results.

The CTA task involves conditioning a novel substance or flavor (i.e., the CS) by pairing it with a malaise that is typically induced after several minutes or hours (e.g., lithium chloride). This association triggers a conditioned aversion, resulting in lower consumption of that flavor. Consumption serves as the measurement of learning utilized during the recall/test session several days after. On the other hand, for the LI of CTA, one PE to the flavor is sufficient to observe the decrease in conditioning, which can easily be compared to that of non-pre-exposed (NPE) subjects.[33] It has been consistently observed that NPE subjects exhibit lower consumption levels compared to those pre-exposed to the CS, demonstrating the effect of the LI of CTA, which significantly established the aversive association (Fig. 1).

The effect of the LI of CTA has been explained through the lens of strength deficits in CS-US association during CTA or through the perspective of PE -induced retrieval/recall impairment. However, according to theories of acquisition alteration, the LI of CTA can hardly be considered as the PE that causes the delay in acquiring conditioning. Since PE prevents the CS-US association, it cannot manifest during the recall/test session, regardless of the time interval. This hypothesis became controversial due to a series of studies that included varying time intervals between the conditioning phase and the test phase.[38] The LI of CTA has shown different degrees of conditioning weakening. Some reports indicate that an increase in LI was observed during aversion memory retrieval after a long interval. This phenomenon, described by De la Casa and Lubow as Super-LI,[39] represents an enhancement of learning that occurs when a pre-exposed stimulus is used in a conditioning task, but under specific experimental parameters that differ from the standard LI procedure. In other words, super-LI is a paradoxical phenomenon where, under specific conditions, PE to a stimulus that is later paired with an outcome enhances learning rather than impairing it as standard LI predicts.

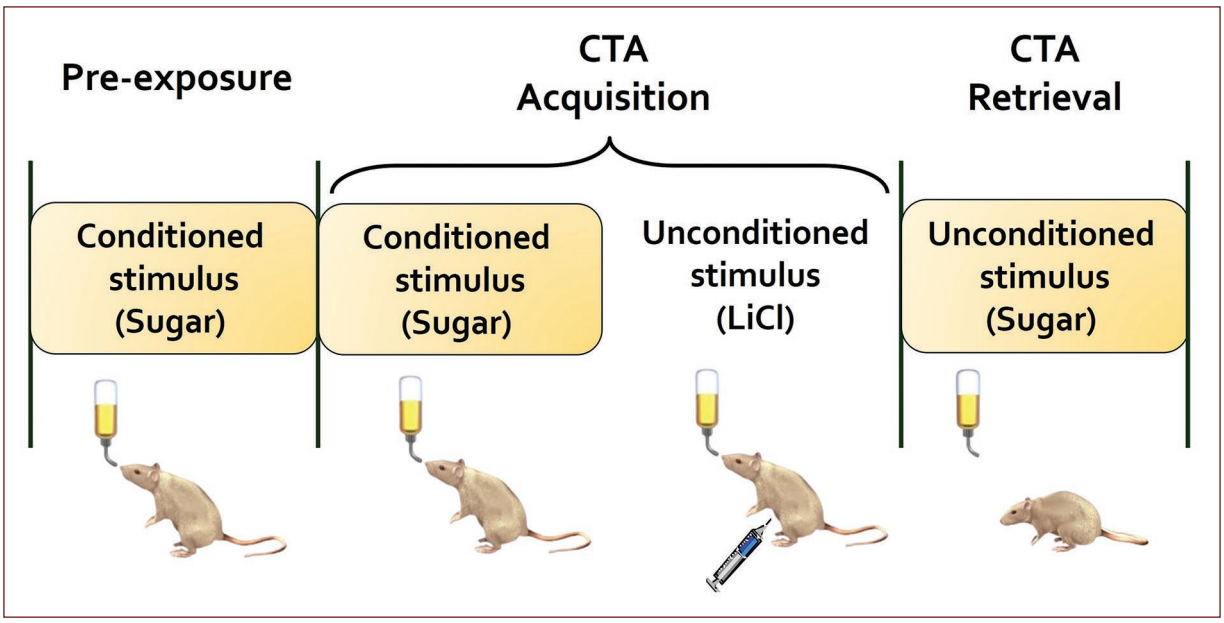

Figure 1. Latent inhibition (LI) of the conditioned taste aversion (CTA) model. The CTA model consists of an initial water deprivation (18 h) to ensure liquid consumption during baseline. Subsequently, experimental groups are established: the pre-exposure group, which receives one or several non-reinforced trials with a palatable flavor (conditioned stimulus), and a second group called the NPE group, which receives the same trials but with exclusive access to water. During the CTA conditioning/acquisition phase, groups are presented with the flavor followed by a substance that produces gastrointestinal irritation (unconditioned stimulus). Next, one day or several days after acquisition, a retrieval memory test is conducted by presenting the flavor again. Consistently, it has been seen that animals in the NPE group consume a significantly smaller amount of the presented flavor compared to the PE group, demonstrating the LI of CTA.

Therefore, the alternative hypothesis of "impaired retrieval of aversive associative memory" has been proposed.[16] This hypothesis indicates that two independent associations are created. The first stems from an initial incidental association of taste and the "absence" of apparent consequences during the PE phase, and the second arises from a conditioned association of taste with gastric discomfort during acquisition. These two associations coexist in a proactive interference process competing with the expression of the CS-US association during conditioning. Later, when the learning test is conducted, the presence of the taste should lead to the recovery of the previously established second association. However, evidence indicates that the recovery of learned associations is carried out based on the order in which they were established, the time interval, and the context in which they occurred.[40] The result is that the first association (stimulus-absence of consequence) interferes with the retrieval of the second (CS-US), manifesting as LI. Conversely, when the learning test is conducted a long time after PE, the interference of the first association is weaker than the second, and a decrease in LI is observed (e.g., Super-LI).

LI as a tool in the study of psychopathological behaviors in humans

Given that the LI phenomenon is highly robust, it has been used in research to assess alterations in attention processes in human psychopathologies, such as schizophrenia,[9] attention deficit disorder, obsessive-compulsive disorders, anxiety disorders, hyperactivity, and certain autism spectrum disorders.[41-46] Specifically, LI has served as a model for the development of potentially valuable psychoactive drugs to treat schizophrenia, since the experimental LI procedure is sufficiently sensitive to identify differences in the ability to ignore irrelevant stimuli.[47] Furthermore, the new salience hypothesis suggests that aberrations in the assignment of salience culminate in hallucinations and unusual beliefs, which are "positive symptoms" of schizophrenia, as evidenced by the research from studies on LI.[8] Thus, current research indicates that LI is attenuated in individuals with schizophrenia and

schizotypy, the multidimensional derivative of schizophrenia. Overall, the evidence suggests that patients assign greater salience to stimuli than individuals with low schizotypy scores and healthy individuals. However, further studies are needed on patients with schizophrenia to avoid or separate the multivariable effects of psychotropic medications, idiosyncratic parsing of samples, variation in dependent variables, and lack of statistical power, all of which have limited and mixed the current results. Moreover, LI experimental designs are restrained by the inconsistent effects or interpretations related to conditioned inhibition, learned irrelevance, priming, novel-relevant effects, and changes in context.

Furthermore, LI is a model used in conditioned food aversion treatments to counteract the side effects of some chemotherapy and radiotherapy procedures in cancer patients[48] and as an alternative treatment for specific conditioned fears and phobias.[49] Similarly, LI has also been used to elucidate the high incidence of abuse of substances such as alcohol and nicotine.[50] In this regard, further studies using LI as a tool can shed light on the complexity of the brain's plastic changes and the neuroadaptations that underlie shifts between impulsive and compulsive behaviors often observed in eating disorders. Continuously isolating irrelevant information favors selective attention to important tasks to better, helping individuals better adapt to their environment and avoid sensory overload. Various neuropsychiatric pathologies, such as schizophrenia, are characterized by a deficit in selective attention, highlighting the importance of LI as a study model for investigating the neurobiological underpinnings of these disorders and developing specific and efficient pharmacological treatments. Novel studies in animal models and human pathologies have furthered our understanding of memory and reinforcement systems. These studies have also led to new questions, particularly regarding how LI of CTA is linked to the uncontrolled consumption of sweet flavors, such as saccharin and sucrose. The current trend of consuming sweet foods leads to stepped preference (i.e., compulsive eating that promotes increased intake of foods lacking essential nutritional value), ultimately contributing to overeating and weight gain. However, it is still necessary to define essential aspects that help process the novelty and relevance of stimuli in different contexts. Furthermore, it is important to define the other variables present in various contexts when familiarizing with rewarding stimuli and highly reinforcing stimuli, such as sweet foods. Assessing the possibility of changing the inherent or learned hedonic load of rewarding stimuli – particularly sweet and caloric foods – through LI is also vital. Future studies addressing these questions, particularly those focusing on the neurobiology of LI in CTA, can help elucidate the complexity of the brain's plastic changes that underlie shifts in eating behavior, including the loss of self-control in individuals who maintain motivation through constant learning processes (PEs), despite severely detrimental health effects.

Conclusion

Evidence indicates that LI is not a unitary, linear phenomenon, as it depends on complex neural mechanisms and behavioral processes. Non-reinforced PEs to a stimulus play a crucial role during learning because they create familiarity through incidental memory. This familiarity establishes an attentional filter that diminishes future associations and influences MS.

This review highlights the importance of assessing, through IL, the essential aspects that facilitate the processing of novelty and relevance in different contexts. In addition, recent studies have provided insight into changes in the inherent or learned hedonic load of rewarding stimuli, like sweet and caloric foods. Future research that addresses these questions by studying the neurobiology of the LI of CTA can help researchers understand the brain's plastic changes that underlie shifts in eating behavior.

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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 to have followed the ethical standards

of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. 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. 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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REVIEW ARTICLE

Idiopathic intracranial hypertension: a literature review

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Abstract

Idiopathic intracranial hypertension is a syndrome characterized by increased intracranial pressure without an identifiable cause. It primarily affects young women and is associated with obesity. Its pathophysiology involves alterations in cerebrospinal fluid (CSF) dynamics, vascular dysfunction, and hormonal and metabolic factors. The main symptoms include headache, papilledema, and visual disturbances, although neuropsychiatric manifestations and sleep disorders may also occur. Diagnosis is based on clinical criteria, neuroimaging such as magnetic resonance imaging and magnetic resonance venography, and measurement of CSF pressure. Diagnostic tools such as optical coherence tomography and transorbital ultrasound have proven useful for diagnosis and monitoring. Treatment varies according to severity and includes lifestyle modification, pharmacological therapy with acetazolamide and topiramate, and, in cases refractory to medical treatment, surgical procedures such as CSF shunting, venous sinus stenting, or optic nerve sheath fenestration. During follow-up, both clinical outcomes and findings from diagnostic tools should be regularly assessed. This narrative review summarizes current evidence and highlights the need for standardized protocols and clearly defined therapeutic goals to improve visual prognosis.

Keywords: *Idiopathic intracranial hypertension. Intracranial pressure. Papilledema. Headache. Ventriculoperitoneal shunt.*

Hipertensión intracraneal idiopática: una revisión de la literatura

Resumen

La hipertensión intracraneal idiopática es un síndrome caracterizado por un aumento de la presión intracraneal sin una causa identificable. Afecta principalmente a mujeres jóvenes y se asocia con la obesidad. Su fisiopatología involucra alteraciones en la dinámica del cefalorraquídeo (LCR), trastornos vasculares, factores hormonales y metabólicos. Los principales síntomas incluyen cefalea, papiledema y alteraciones visuales, aunque pueden presentarse manifestaciones neuropsiquiátricas y trastornos del sueño. El diagnóstico se basa en criterios clínicos, neuroimagen como la resonancia magnética y venografía por resonancia magnética y medición de la presión del LCR. Auxiliares diagnósticos como la tomografía de coherencia óptica y el ultrasonido transorbital han mostrado utilidad en el diagnóstico y monitorización. El tratamiento varía según la gravedad, incluyendo modificación del estilo de vida, fármacos como acetazolamida y topiramato, y en casos refractarios al tratamiento médico, procedimientos quirúrgicos como derivaciones de LCR, colocación de stents venosos o la fenestración

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de la vaina del nervio óptico. Durante el seguimiento se deben evaluar resultados de los pacientes clínicos y mediante auxiliares diagnósticos. Esta revisión narrativa sintetiza la evidencia actual y resalta la necesidad de protocolos estandarizados y objetivos terapéuticos definidos para mejorar el pronóstico visual.

Palabras clave: *Hipertensión intracraneal idiopática. Presión intracraneal. Papiledema. Cefalea. Derivación ventriculoperitoneal.*

Introduction

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by increased intracranial pressure (ICP) without an identifiable underlying cause. It is defined as elevated ICP (> 25 cm H_2O).[1,2] Its incidence ranges from 0.03 to 7.8 cases/100,000 people and is more common in women. Although its etiology remains unclear, IIH is considered a multifactorial disorder potentially linked to abnormalities in cerebrospinal fluid (CSF) production and absorption, vascular dysfunction, and hormonal or metabolic factors.[1,3]

IIH is characterized by headache, papilledema, and increased ICP, though its clinical presentation varies from non-specific symptoms to severe neurological impairment.[1,2] Diagnosis requires the systematic exclusion of secondary causes of intracranial hypertension. It is based on the integration of clinical and paraclinical findings, including signs of elevated ICP, CSF opening pressure measurement through lumbar puncture (LP), and neuroimaging findings. Treatment aims to lower ICP, preserve visual function, and prevent irreversible complications, using pharmacological or surgical approaches when necessary.[2,4]

Understanding the risk factors and pathophysiology of IIH improves the recognition of its clinical manifestations, aiding in the development of diagnostic and follow-up strategies. A comprehensive review of these aspects helps identify knowledge gaps and guide future research. This review examines pathophysiological mechanisms, classical and atypical clinical manifestations, diagnostic criteria, auxiliary studies, treatment approaches, and prognosis.

Methods of the review

To perform this narrative review, a structured literature search was conducted to identify meta-analyses, clinical trials, cohort studies, multicenter studies, and pre-clinical studies that provide recent evidence on the epidemiology, pathophysiology, diagnosis, and treatment of IIH. The search was performed in PubMed, Scopus, and Web of Science, using combinations of the keywords "idiopathic intracranial hypertension OR pseudotumor cerebri," "pathophysiology," "risk factors," "diagnosis," "treatment," and "outcomes" from January to June 2025. Given the exploratory nature of this literature review, no strict exclusion criteria were applied, allowing the inclusion of all potentially relevant studies that contributed to a comprehensive and updated overview of the current scientific knowledge on IIH. Nevertheless, priority was given to the inclusion of meta-analyses, systematic reviews, randomized controlled trials, cohort studies, and multicenter research. No language restrictions were applied.

Epidemiology

The epidemiology of IIH shows considerable geographic and temporal variation depending on the studied population, diagnostic criteria, and study year. Reported incidence rates range from 0.03/100,000/year in Japan to 2.36/100,000/year in Northern Ireland. A meta-analysis including 15 population-based studies estimated a pooled annual incidence of 1.20/100,000, although heterogeneity was high (I^2 = 98%). Age- and sex-specific analyses indicate that women aged 14-45 years have a markedly higher incidence, ranging from 0.65/100,000/year in Italy to 10.3/100,000/year in Libya.[2-4]

When stratified by study period, incidence rates increased from 0.84/100,000/year before 2000 to 1.90/100,000/year after 2000, consistent with the global rise in obesity prevalence. According to data from the World Health Organization, IIH incidence is strongly correlated with national obesity rates (Spearman's $r = 0.82$, $p < 0.01$).[2,4] Subgroup analyses demonstrated a progressive increase in IIH incidence with higher obesity prevalence: 0.14/100,000 for countries with obesity < 10%, 0.77/100,000 for 10-20%, and 1.48/100,000 for > 20%.[1,3,4] These findings highlight the close epidemiologic relationship between IIH and obesity, particularly among women of reproductive age.

Pathophysiology

Increased CSF production

The choroid plexus regulates CSF secretion through ion transporters such as NKCC1 and AQP-1.

Experimental studies suggest that androgens, adipokines, and glucocorticoids may upregulate NKCC1 and AQP-1 activity, increasing CSF production. Studies in rats have shown that testosterone administration stimulates NKCC1, leading to higher CSF secretion. In addition, obese rats exhibit elevated AQP-1 expression, linking obesity to altered CSF dynamics.[2,3,5]

Impaired venous drainage

The arachnoid granulations (AGs) facilitate CSF absorption into the dural venous sinuses. In IIH, enlarged or insufficient AGs may obstruct venous outflow, raising sinus pressure and further impairing CSF clearance. Studies show that women with IIH have fewer AGs than controls, which may reduce their capacity to compensate for increased ICP.[2,3,6]

Venous sinus stenosis

Venous sinus stenosis, particularly in the transverse sinus, occurs in 23-93% patients with IIH, compared to 5-7% in the general population. Stenosis can be intrinsic, caused by fibrotic membranes or enlarged AGs, or extrinsic, resulting from ICP elevation that compresses the sinus wall.[3-7] A self-sustaining feedback loop may exist, where increased ICP worsens stenosis, which in turn elevates ICP further. Distinguishing between primary and secondary stenosis is crucial for tailoring treatment approaches.[3,6]

CSF lymphatic and glymphatic drainage

Experimental studies have proposed that lymphatic drainage may serve as an alternative pathway for CSF absorption, challenging the belief that the CNS lacks a functional lymphatic system.[1,2,6] Experimental models have shown that CSF outflow occurs through perineural routes to cervical lymph nodes and through spinal nerves into epidural lymphatics, with the olfactory nerve being the primary drainage route in animal models.[2,5,6]

The glymphatic system, primarily regulated by aquaporin-4 (AQP4) channels in astrocytic end-feet, is thought to facilitate CSF-interstitial fluid exchange and metabolic waste clearance.[3] Dysfunction of this system has been implicated in toxin accumulation and various neurological disorders. In IIH, glymphatic and lymphatic dysfunction, together with impaired venous outflow, have been hypothesized to contribute to CSF dysregulation.[2,3,7] Small magnetic resonance imaging (MRI)-based studies in humans have reported increased extraventricular CSF and interstitial fluid volumes, findings consistent with altered CSF homeostasis, though causality remains unproven.[3-7]

At the molecular level, alterations in AQP4 expression, NKCC1 activity, and hormonal or adipokine regulation have been experimentally associated with changes in CSF dynamics. However, most of these data derive from pre-clinical or animal studies, and their translation to human IIH pathophysiology is not yet established. The observed association of IIH with female sex and obesity suggests a potential link to endocrine, inflammatory, or metabolic mechanisms, but further research is needed to confirm these hypotheses.[2-7]

Clinical manifestations

The most common manifestations of IIH are headaches and papilledema, which can cause varying degrees of visual impairment, and other symptoms such as pulsatile tinnitus, nausea, vomiting, and neck or back pain.[3]

Headache

Headache is the most common symptom, affecting 75-94% of IIH patients. Its presentation varies, ranging from persistent to intermittent and pulsatile to pressure-like, often worsening with coughing or the Valsalva maneuver. Up to 45% have a history of migraine, and over 80% experience headache with a migraine phenotype.[3,8]

Visual manifestations

Transient visual obscuration is common, and in patients without papilledema, symptoms such as photopsia, diplopia, and enlargement of the blind spot can occur, though less frequently. Papilledema is the most common manifestation after headache, affecting both eyes symmetrically. The gold standard for grading papilledema is the Frisén scale,[3,8,9] as shown in table 1.

Others

Neuropsychiatric symptoms occur in up to 86% of patients, with the most common being depression and anxiety in 83%, mild depression in 61%, and moderate or severe depression in 59%. Mild anxiety is present in 67%, eating or appetite disorders in 76%, and

Table 1. Modified Frisén scale

Grade 1 (minimal papilledema)	A subtle C-shaped halo appears at the nasal border, without blurring of the temporal margin
Grade 2 (mild papilledema)	The halo encircles the entire optic disc, with an elevation of the nasal border
Grade 3 (moderate papilledema)	Obscuration of at least one segment of a main vessel at its exit from the disc, with the entire border elevated
Grade 4 (marked papilledema)	Complete obscuration of a main vessel at its exit from the disc, with elevation of the entire optic nerve head and obscuration of the border
Grade 5 (severe papilledema)	Partial or total obscuration of all blood vessels of the optic disc and leaving the disc

Adapted from García-Ull et al.[9].

apathy and irritability in 20%. In addition, 45% are diagnosed with a concurrent psychiatric disorder. The most common disorders were major depressive disorder (24.3%) and anxiety/stress-related disorders (24.3%). Depression correlates with younger age, higher body mass index (BMI), and headaches without visual symptoms.[10]

Some studies have found that patients with IIH performed significantly worse on various neuropsychological tests. 24.8% of patients show impairment across multiple domains, particularly in processing speed, working memory, sustained and complex attention, set shifting, and confrontation naming, compared to controls in measurements taken at 3, 6, and 12 months.[11]

Sleep apnea-hypopnea syndrome affects 33-63% of people with IIH. It is associated with worsening symptoms such as headaches, cognitive impairment, and neuropsychiatric symptoms, as well as increased ICP, likely due to various mechanisms, including hypoxia and hypercapnia resulting from cerebral vasodilation and increased cerebral blood flow.[12]

Other less common presentations of the disease include unilateral papilledema, present in 1.4% of cases, IIH without papilledema, involvement of cranial nerves (abducens, oculomotor, trochlear, trigeminal, or facial), CSF leaks, and recurrent meningitis associated with temporal lobe epilepsy.[13]

Diagnosis

The diagnostic approach to IIH has evolved substantially since the initial description of the Dandy criteria in 1937, reformulated as formal diagnostic criteria by Smith in 1985.[14] These criteria are detailed in table 2.

Currently, the modified criteria proposed by Friedman et al.[15] in 2013 are considered the gold standard for diagnosis. These criteria integrate clinical presentation, CSF findings, and characteristic neuroimaging features, thereby improving diagnostic accuracy and ensuring exclusion of secondary causes. The Friedman 2013 criteria are detailed in table 3.

Given that IIH is defined by elevated ICP without an identifiable cause, it is essential to exclude secondary forms of intracranial hypertension before confirming the diagnosis. These include drug-induced, infectious, endocrine, or systemic conditions known to increase ICP, as well as primary headache disorders such as migraine, which may mimic IIH-associated headache when papilledema is absent or has resolved.[16-20] Table 4 summarizes the main secondary causes that should be systematically ruled out during the diagnostic evaluation.

LP CONSIDERATIONS

Although LP remains a valuable procedure for confirming elevated ICP and excluding secondary causes, it is not always essential for establishing the diagnosis, particularly in patients with typical clinical and neuroimaging features of IIH, where invasive testing may be deferred or contraindicated.[21,22] When performed, CSF opening pressure should be measured with the patient in the lateral decubitus position, with the neck and knees gently flexed and breathing normally, avoiding Valsalva maneuvers or hyperventilation. This position yields the most accurate measurement and reduces the risk of post-dural puncture headache. The needle should be introduced at the L3-L4 or L4-L5 interspace, maintaining the bevel parallel to dural fibers to minimize trauma.[21,23]

In patients with obesity or distorted spinal anatomy, identification of surface landmarks can be challenging; in such cases, pre-procedural ultrasound guidance significantly increases the likelihood of first-attempt success and reduces procedural time. Deep sedation should be avoided, as it can alter CSF pressure, though mild anxiolysis may be considered when patient cooperation is difficult. Accurate interpretation of the opening pressure requires consideration of patient position, anxiety, and abdominal compression, which can transiently elevate readings.[23,24]

Table 2. Modified Dandy criteria

Signs and symptoms of increased intracranial pressure, including headaches, visual disturbances, and papilledema
Absence of focal neurological signs, except for unilateral or bilateral abducens nerve palsy
Elevated opening pressure of CSF, > 25 cm H_2O, with normal CSF composition
Normal or small, symmetrical ventricles on imaging, without intracranial mass or venous obstruction
No other cause of increased intracranial pressure

CSF: cerebrospinal fluid.
Adapted from Pan et al.[14].

Table 3. Diagnostic criteria for idiopathic intracranial hypertension

Required for diagnosis: Papilledema Normal neurologic examination except for cranial nerve 6 abnormalities Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used Normal CSF composition Elevated lumbar puncture opening pressure (> 25 cm H_2O in adults and > 28 cm H_2O in children [25 cm H_2O if the child is not sedated and not obese])
Diagnosis without papilledema: Diagnosis made if B-E from above are satisfied, and the patient has a unilateral or bilateral abducens nerve palsy Suggested diagnosis if B-E from above are satisfied, and in addition, at least 3 of the following neuroimaging criteria are satisfied: Empty sella Flattening of the posterior aspect of the globe Distention of the perioptic subarachnoid space with or without a tortuous optic nerve Transverse venous sinus stenosis

CSF: Cerebrospinal fluid, MRI: magnetic resonance imaging, CT: computed tomography.
Adapted from Pan et al.[14].

Auxiliary diagnostic

Auxiliary diagnostic studies are part of the diagnostic criteria and help exclude other causes of increased ICP. Brain MRI is the most commonly used imaging method. However, studies have also described the use of transorbital ultrasound (TOS), optical coherence tomography (OCT), and OCT angiography (OCT-A).[25]

Neuroimaging

The primary goal of neuroimaging in patients with suspected IIH is to rule out other causes of intracranial hypertension. Neuroimaging identifies patterns suggestive of increased ICP, with abnormal findings in 92.5% of cases. The most frequent signs include an "empty" sella turcica (68.8%), optic nerve tortuosity (82.5%), posterior flattening of the eyeball and sclera (80%), dilatation of the periorbital subarachnoid space (73.8%), and hyperintensity of the optic nerve head (20%). In addition, distension of the optic nerve sheath, slit-like ventricles, narrowing of the subarachnoid spaces, downward displacement of the cerebellar tonsils, posterior displacement of the pituitary stalk, and meningocele may also be observed.[26,27]

The sensitivity and specificity of individual signs vary, and sensitivity increases when a combination of signs is observed. Prabhat et al. found that optic nerve tortuosity was the most sensitive (82.5%), and the most specific signs were posterior scleral flattening and peripodic dilatation of the subarachnoid space (96.6%).[27] Arkoudis et al.[28] proposed the acronym "STOP" to facilitate recall of key neuroimaging findings: S: empty sella, T: transverse sinus stenosis, O: optic nerve sheath distension, P: posterior globe flattening. It aims to highlight essential signs not to be overlooked. In addition to MRI, magnetic resonance venography should be performed to detect venous sinus stenosis.[29-33]

Transorbital sonography

The use of ultrasound has been proposed as a non-invasive alternative for measuring ICP. Different ultrasound modalities, such as transcranial Doppler, transorbital Doppler, and transorbital B-mode, are used for diagnostic and monitoring purposes.[34,35]

TOS is the most frequently used modality, allowing the evaluation of optic nerve sheath diameter (ONSD) and optic disc elevation (ODE) in patients with IIH. Patients exhibit larger diameters compared to healthy controls.[35-38] A meta-analysis conducted by Janitschke et al. found that the ONSD was significantly larger in patients with IIH compared to controls (standardized mean difference 2.5 mm, 95% confidence interval [CI] 1.6-3.4). They also reported a 95% prevalence (95% CI 92-97%) of papilledema, with a cutoff point ranging from 4.3 to 6.3 mm, showing sensitivity of 70-100% and specificity of 67-100% for diagnosing papilledema.[39]

Table 4. Auxiliary diagnostics

Auxiliary diagnostic	Clinical role	Finding	Sensitivity	Specificity
MRI	Diagnosis	Empty sella turcica[28] Partially empty sella[28] Meckel's cave enlargement[28] Optic nerve tortuosity[28] Optic nerve sheath distension[28] Optic nerve enhancement[28] Optic nerve head protrusion[28] Transverse sinus stenosis[28] Posterior displacement of pituitary stalk[28] Posterior globe flattening[28] DWI bright spot at fundus[28] Slit-like ventricles[28] Tight subarachnoid spaces[28]	26.7-70% 43-92% 9-75% 60% > 84% 6.7-50% 3.3-37.2% 62.8-73% 39.5% 43.3-80% 9.5-26.3% 3-39.5% 0-3%	94.3-95% 74-100% 59-100% > 95% 100% 98.2-100% 95-100% 92-97% 90.7% 95-100% 99-100% 79.1-100% 0-100%
MRV	Diagnosis Screening to determine candidacy for catheter venography[26] Monitoring[29]	Transverse sinus stenosis[29,30] Transverse sinus stenosis was identified using the ITSS based on bilateral narrowing assessment[31], the quantitative semi-automatic measurement (QSAM) that measures the stenosis percentage through diameter[32], and the CAD that quantifies cross-sectional areas and volumes[33].	93-100%[29,30] 94.7-100%	33.3-93%[29,30] 93.3-100%
TOS	Diagnosis	ONSD as a predictor of increased intracranial pressure, with 5.7 mm as the cutoff value[38] ONSD with cutoff value 4.3-7.3 mm[39]	90% at the right eye and 91% at the left eye[38] 70-100%[39]	80 at the right eye and 80% at the left eye[38] 67-100%[39]
OCT	Diagnosis Monitoring[42]	An average peripapillary RNFL thickness ≥ 110 μm, or ≥ 150 μm in the inferior quadrant, may help distinguish true papilledema from pseudopapilledema (population with no IIH diagnosis)[43]	70% to ≥ 110 μm[43] 67% to ≥ 150 μm[43]	77% to ≥ 110 μm[43] 80% to ≥ 150 μm[43]

CAD: computer-assisted detection; DWI: diffusion-weighted imaging; MRI: magnetic resonance imaging; MRV: magnetic resonance venography; OCT: optical coherence tomography; OCT-A: optical coherence tomography angiography; ONSD: optic nerve sheath diameter; IIH: idiopathic intracranial hypertension; ISS: index of transverse sinus stenosis; RNFL: retinal nerve fiber layer; TOS: transorbital ultrasound; QSAM: quantitative semi-automatic measurement.

Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCT-A)

Both modalities allow for qualitative and quantitative evaluation of changes in the retinal nerve fiber layer (RNFL), the optic nerve head, the macula, and retinal and choroidal perfusion. OCT is useful for identifying and monitoring papilledema, as it provides structural information about the retina and choroid, enabling visualization of optic nerve head inflammation and assessment of the retinal pigment epithelium/Bruch's membrane layer. OCT-A offers data on retinal and choroidal vasculature and blood flow, as well as enabling the evaluation of vascular density in the optic disc and the peripapillary region.[40,41]

Several studies have analyzed the usefulness of these techniques as diagnostic tools and for assessing treatment response in patients with IIH. In diagnostic and therapeutic monitoring contexts, the most frequently evaluated parameters include retinal RNFL thickness, optic nerve head volume and height, and optic disc border and area, all of which tend to show greater alterations in IIH patients compared to healthy controls. However, no standardized cutoff value exists for OCT or OCT-A to date.[41-43] Table 5 shows a summary of the main characteristics of auxiliary diagnostics.

Treatment

Treatment includes lifestyle modifications (weight loss), pharmacological therapy, and surgical interventions for refractory cases. Treatment guidelines outline three key principles: addressing the underlying condition through weight reduction, preserving vision, and alleviating headache burden.[44]

Medical treatment

Treatment of IIH includes the use of diuretics such as acetazolamide or furosemide, as well as topiramate,

Table 5. Conditions and drugs to exclude (secondary intracranial hypertension)

Causes	Description
Associated disorders[16-19]	Infections Hormonal disorders: polycystic ovary syndrome Obesity: adolescent and adult obesity Anemia Micronutrient disorders: Vitamin A, B1, and B12 deficiency, hypervitaminosis A OSAHS
Medications Associated with Increased ICP[20]	Vitamin A derivatives Antibiotics: tetracyclines, second- and third-generation fluoroquinolones, sulfadiazine Steroids: corticosteroids, stanozolol Contraceptives: progestin-only, combined oral contraceptives Hormonal agents: GnRH agonists, LHRH agonists, danazol Nalidixic acid, amiodarone, valproic acid, sulfasalazine, cyclosporine, ketoconazole, ustekinumab

IIH: idiopathic intracranial hypertension; ICP: increased intracranial pressure; OSAHS: obstructive sleep apnea-hypopnea syndrome; GnRH: gonadotropin-releasing hormone; LHRH: luteinizing hormone-releasing hormone.

octreotide, and occasionally corticosteroids. Repeated LPs may be performed as a temporizing measure to relieve ICP, but they do not represent definitive therapy and are generally reserved for special circumstances, such as pregnancy. The main therapeutic goal is to prevent vision loss and preserve neurological function.[21,44] Acetazolamide is a carbonic anhydrase inhibitor and remains the first-line pharmacologic treatment for IIH. Its primary therapeutic goal is the preservation of visual function[45]. It reduces CSF secretion by inhibiting carbonic anhydrase and modulating ion transport in the choroid plexus, including Na^+/K^+-ATPase activity. The usual starting dose is 250-500 mg twice daily, titrated up to a maximum of 4 g/day. Common adverse effects include paresthesia, fatigue, loss of appetite, dysgeusia, gastrointestinal disturbances, electrolyte imbalance, tinnitus, and rarely nephrolithiasis.[3,44] There is no standardized treatment duration established by any consensus. However, current studies report a treatment period ranging from 6 months to 1 year. During the first 6 months, therapy and dietary modification led to a reduction in CSF opening pressure, a decrease in papilledema grade, improvement in visual field and quality of life, and a slight improvement in visual acuity and headache. The most significant overall improvement is observed at 12 months of treatment.[45,46]

Topiramate may be beneficial in patients with IIH, particularly given the high prevalence of obesity and migraine in this population. Although evidence remains limited, available data suggest a favorable effect on headache control and weight reduction. Topiramate is thought to modestly reduce CSF production, thereby contributing to ICP lowering, while its appetite-suppressing properties promote weight loss. Typical doses range from 50 to 200 mg daily. However, it should not be considered equivalent in efficacy to acetazolamide. Reported adverse effects include nausea, paresthesia, dizziness, drowsiness, cognitive disturbances, tremors, blurred vision, or diplopia.[21]

Similar to acetazolamide, the duration of topiramate therapy remains undefined. However, current evidence suggests a treatment period of 6-12 months, occasionally extending to 23 months in selected cases. A recent meta-analysis reported significant headache improvement after 3 months, with progressive reduction up to 6 months, as well as visual field and pain score improvement during the same period.[46]

Furosemide is a diuretic that helps decrease CSF production and reduce ICP, and it is used as an adjunctive therapy in patients with IIH. Some authors recommend a maximum dose of 50 mg twice daily, preferring it when previous medications are poorly tolerated.[21,44]

There is limited evidence supporting the use of corticosteroids in the management of elevated ICP across different etiologies. The CRASH-1 trial, conducted in adults with traumatic brain injury, demonstrated an increased mortality risk with intravenous corticosteroid administration and therefore does not directly apply to IIH. In IIH, steroids are not routinely recommended. They should be considered only in exceptional, short-term, vision-threatening situations, such as acute and severe visual loss when immediate reduction of ICP is required before definitive therapy can be initiated. Outside these scenarios, corticosteroids should generally be avoided.[44,47]

Some pharmacologic options remain under investigation and currently have limited evidence in IIH. Glucagon-like peptide-1 receptor agonists have shown preliminary and promising results, but their benefit appears to be primarily mediated by weight loss rather than a direct reduction of ICP.[3,21] Experimental studies suggest that exenatide may reduce CSF secretion, although clinical confirmation is still lacking. In small patient series, semaglutide and liraglutide, when combined with dietary interventions and acetazolamide, have been associated with significant weight reduction

(≥ 10% of baseline body weight), accompanied by improvement in headache and papilledema.[21]

11β-HSD1 inhibitors and prostaglandin analogs are therapies under investigation for IIH. AZD4017, evaluated in a phase II trial, demonstrated good tolerance, cholesterol reduction, and an increase in high-density lipoproteins, showing potential for metabolic control and weight reduction. Intranasal latanoprost may modulate lymphatic contractility by increasing CSF outflow through AGs and nasal lymphatic vessels, helping to reduce ICP.[3,21]

Surgical treatments

Available surgical options include lumboperitoneal (LPS) or ventriculoperitoneal (VPS) shunt insertion, optic nerve sheath fenestration (ONSF), venous sinus stenting (VSS), and bariatric surgery.[48,49]

CSF shunting procedures

CSF shunting is reserved for patients who do not respond to medical therapy, patients who are intolerant or non-compliant with maximum medical treatment, and those who experience visual symptoms worsening.[48,50] It remains the most frequently performed surgical intervention for IIH, used in nearly 90% of surgically treated cases,[48,49] with a greater preference for VPS over LPS. Both techniques are associated with significant improvement in visual symptoms and headache relief, with comparable rates of complications and post-operative follow-up requirements.[48]

A meta-analysis found that the most significant improvement was observed in papilledema in 96% of patients treated with CSF shunting, whereas headache showed substantial improvement in 91%, and visual symptoms improved in 85% of cases.[49] Despite its efficacy, shunt revision remains a major concern occurring in up to 42% of patients, though rates tend to decline over time. Revisions are more frequent with LPS, averaging 4.7 revisions/patient, compared with 1.3/patient in VPS. The leading cause of revision is shunt obstruction, particularly distal catheter blockage (82.1%), followed by proximal obstruction (10.7%) and valve malfunction (7.1%).[49] Patients with a higher BMI have a significantly greater likelihood of requiring shunt revision within the first 30 post-operative days.[51]

While LPS effectively lowers ICP and relieves symptoms by reducing venous and meningeal distension, it may cause low-pressure complications from excessive CSF drainage. The introduction of programmable valves, narrow-lumen catheters, and anti-siphon devices has improved symptom control, underscoring the need for continued evaluation of new shunt technologies to optimize outcomes and minimize adverse effects.[48]

VSS

VSS is a surgical procedure used to treat IIH, with high technical and clinical success, low complication rates.[52] Indications for VSS include refractoriness to medical therapy, imminent visual threat, intrinsic or extrinsic stenosis of the transverse sinuses, and a trans-stenotic gradient ≥ 8 mmHg.[53] All patients undergoing VSS undergo a computed tomography scan to rule out intracranial hemorrhage. Patients will be on dual antiplatelet therapy for 1 month and aspirin 325 mg for 3 months. A follow-up angiography is performed at 3 months to evaluate for possible complications.[54]

VSS has been associated with significant hemodynamic and clinical improvement in IIH. Following the procedure, the trans-stenotic pressure gradient typically decreases from about 18.5-3.4 mmHg, and the CSF opening pressure drops from approximately 37.5-22.3 cmH_2O. Clinically, improvement is reported in pulsatile tinnitus (95%), papilledema (89%), visual disturbances (88%), and headache (79%), supporting VSS as an effective therapeutic option for symptom relief and pressure normalization.[52,55]

During the procedure, a major complication rate of 3.93% has been reported, including 0.65% subdural hematoma, 0.28% subarachnoid hemorrhage, 1.41% worsening of headache, 0.56% visual deterioration, 0.09% worsening of papilledema, 0.47% amaurosis, 0.09% arterial dissection, and 0.38% mortality. The rate of minor complications and adverse events was 2.72%, with 0.09% headache, 1.88% retroorbital pain, and 0.18% neck hematoma.[52]

Juxta-stent stenosis, occurring proximally or distal to the implanted stent, represents a recognized cause of treatment failure or the need for revision following VSS. It has been linked to elevated ICP, persistent pressure gradients, external compression, sinus wall laxity, and uncontrolled reendothelialization. In pooled analyses, the overall complication rate remains below 2%, with an estimated stent survival of 84% and adjacent stenosis observed in approximately 14% of patients at 20 months of follow-up, emphasizing the need for long-term surveillance to detect progressive venous narrowing.[56]

Reported outcomes after VSS show that IIH recurs in about 9% of patients, with few requiring repeated endovascular treatment or CSF shunting. Across pooled data, 6-7% develop new complications, and 20-25% experience persistent or recurrent symptoms during follow-up. Restenosis occurs within or near the stent in roughly 17.7% of cases.[57]

Comparative studies of open-cell (OC) and closed-cell (CC) stents have shown similar safety and efficacy. The OC group reported a failure rate of 8%, with improvement in 78% of patients for headache and visual acuity and 88% for papilledema, without complications. The CC group had a failure rate of 5%, with 81% improvement in headache, 76% in visual acuity, and 82% in papilledema. Major complications occurred in 2% of cases, while no minor events were reported, supporting both designs as safe and effective options.[58]

Evidence suggests that the pressure gradient across the stenotic segment is a key predictor of visual recovery following VSS. In a cohort, a three-item model incorporating pre-operative pressure gradient, degree of stenosis, and papilledema severity demonstrated moderate accuracy in identifying patients with a slower response to treatment, with 72% sensitivity and 73% specificity. Faster improvement was linked to lower pre-operative gradients, less severe stenosis, and milder papilledema.[59] Subsequent analyses confirmed that lower pre- and post-operative gradients independently predicted favorable outcomes (Frisén score 0-1), underscoring the value of hemodynamic assessment in optimizing patient selection and anticipating therapeutic response.[60]

Acute restenosis is a complication that occurs in approximately 18% of cases.[57] However, only about 10% become symptomatic or require retreatment or stent extension. In a patient series of in-stent stenosis, few patients have required intervention.[54] Management involves thrombolytic therapy with anticoagulation or repeated stenting to extend the affected segment. Although treatment is individualized, reintervention is usually considered when there is a significant increase in the pressure gradient (~48 cmH_2O) or a stenosis of around 65%.[61,62] At present, no standardized criteria exist for the management of restenosis, which highlights the need for long-term follow-up studies and consensus guidelines to define optimal therapeutic approaches.

ONSF

ONSF reduces intraocular pressure by incising the anterior dural sheath of the optic nerve, allowing CSF to drain and relieving pressure around the retrobulbar segment.[63,64] It is indicated in cases of imminent visual loss due to elevated ICP when other treatment options have failed or are contraindicated. A TOS is useful in determining surgical candidacy, typically demonstrating retrobulbar optic nerve sheath dilation > 6 mm. This finding can also be visualized on high-resolution T2-weighted orbital MRI sequences.[65]

A less invasive alternative, endoscopic nasal optic nerve decompression, involves removal of the bony wall surrounding the optic canal through an endonasal sphenoid approach to relieve compression and restore blood flow.[66] Reported outcomes show improvement in headache (78%), papilledema (72%), and visual disturbances (88%), with greater efficacy observed in unilateral procedures and when combined with ONSF.[67]

ONSF significantly improves visual outcomes in IIH. A recent meta-analysis reported notable recovery in visual field performance and reduction of optic disc inflammation after surgery, with slightly higher success rates for the transconjunctival approach.[68] Across surgical techniques, visual acuity and field improvements are consistently observed, with success rates of 90-94%. Papilledema and optic disc edema resolve in most cases, with improvement in 77-97% of patients, favoring the transconjunctival method.[68-70]

Early intervention is critical, as prompt surgery is associated with better visual outcomes and prevention of irreversible optic nerve atrophy. Once atrophy develops, visual recovery becomes unlikely, emphasizing the need for timely diagnosis and management. Post-operative monitoring remains essential, since recurrence of symptoms occurs in up to 32% of cases.[68]

Among the post-operative outcomes, visual function assessed by automated perimetry showed a significant improvement at 1 and 6 months, whereas visual acuity demonstrated a marked improvement at 6 months, with no notable changes during the early post-operative period (1 week to 1 month). A significant bilateral reduction in papilledema was observed after 2 weeks, with progressive recovery at 3, 6, and 12 months, as measured by the Frisén scale. Optic nerve head morphology also changed within weeks, as demonstrated by Heidelberg OCT measurements. Headache resolution occurred in about 49% of patients, with better results after bilateral surgery, likely due to greater reduction of ICP through enhanced CSF filtration.[71]

Interventions for weight reduction

Weight reduction is a key component in the management of IIH, as it correlates with decreased ICP.

Treatment strategies include dietary interventions, lifestyle modifications, and bariatric surgery. In the short term, dietary interventions achieve modest BMI reductions (2-2.3 kg/m^2 over 3-6 months), whereas bariatric surgery results in 27.2-27.8 kg of weight loss at 24 months, with gastric bypass achieving the highest reduction (69.9-71% of total body weight). Bariatric surgery led to the greatest CSF-ICP reduction, followed by multicomponent lifestyle interventions with acetazolamide and very low-energy diets. In addition, it was associated with papilledema resolution (100%), headache improvement (90.2%), and a BMI reduction of up to 17.5 kg/m^2.[72,73]

Management of fulminant IIH

Fulminant IIH is a rapid vision-degrading presentation of IIH with limited published studies. It predominantly affects women (95.8%) and may also occur in patients with normal BMI, sometimes in the absence of headache. A review of published cases found that 11% of patients with fulminant IIH did not undergo surgical intervention. Among these, 45% had anemia and were treated with iron supplementation alone or in combination with acetazolamide. However, surgical treatment is recommended for patients at risk of visual loss.[74]

The most frequently reported surgical procedures include ONSF (36.1%), LPS (25%), VPS (13.9%), and VSS (12.5%). Most studies used perimetry as the primary outcome. However, there was considerable variability in both methodology and timing of assessments, which ranged from 3 weeks to 8 months, with progressive visual improvement observed in patients managed with pharmacological treatment or surgery[74].

Prognosis

The most frequent course of disease is slow progression over a period of months or even years. If treatment is effective, prognosis is usually favorable, with symptoms improving and stabilizing. Some patients continue to present with papilledema, high ICP, and even mild residual visual deficits. The main predictors of poor prognosis include moderate-to-severe papilledema (Frisén scale 3-5) and vision loss, with or without other visual symptoms. Additional risk factors are male sex, black race, younger age of onset or onset during puberty, elevated opening pressure, severe obesity or significant weight gain, and high blood pressure.[16] Weight loss plays a crucial role in slowing disease progression, although standardized monitoring and follow-up protocols are still lacking.[49]

Monitoring

Currently, there are no established consensus guidelines regarding the duration of patient follow-up. However, most cohort studies conduct evaluations at 1, 3, 6, and 12 months, showing progressive improvement over this period. This timeframe appears reasonable for the monitoring of symptom recurrence or papilledema reappearance.[72,75]

The main follow-up outcomes most frequently reported include ICP measurements (LP, telemetric ICP monitoring), headache (questionnaires such as monthly headache days or monthly moderate-to-severe headache days), visual function (automated perimetry, visual acuity), papilledema (Frisén scale, OCT imaging), and OCT measurements as indicators of visual function, along with patient-reported outcomes (questionnaires such as 10-Item Neuro-Ophthalmic Supplement, 25-Item National Eye Institute Visual Function Questionnaire, 6-Item Headache Impact Test, Short Form-36, EQ5D, and the Hospital Anxiety and Depression Score) and patient reported outcome of the most bothersome symptom.[75]

Recurrence, defined as the reappearance of papilledema or symptoms consistent with IIH accompanied by elevated opening pressure, has been reported in 8% to 38% of patients, often occurring years after sustained remission or clinical stability. The main predisposing factor identified is weight gain.[16]

Onyia et al.[76] proposed a risk-based monitoring approach for IIH to guide follow-up according to disease severity and the likelihood of visual loss. Monitoring should include fundus examination, visual field testing, and OCT, whereas ICP assessment is reserved for selected cases. In this model, patients are classified as low, intermediate, high, or indeterminate risk. Low-risk patients, who show no visual impairment or papilledema and may present only with headache, are reviewed every 3-6 months. Intermediate-risk cases, characterized by mild, stable, or slowly progressive visual field defects or mild papilledema, require evaluations every 1-3 months, including periodic LP.

High-risk patients, with rapidly worsening or severe visual loss and moderate-to-severe papilledema, must be monitored closely every 1-4 weeks, ideally with continuous ICP recording and imaging to assess optic nerve recovery. Those in the indeterminate-risk group, such as individuals with recurrent or persistent disease

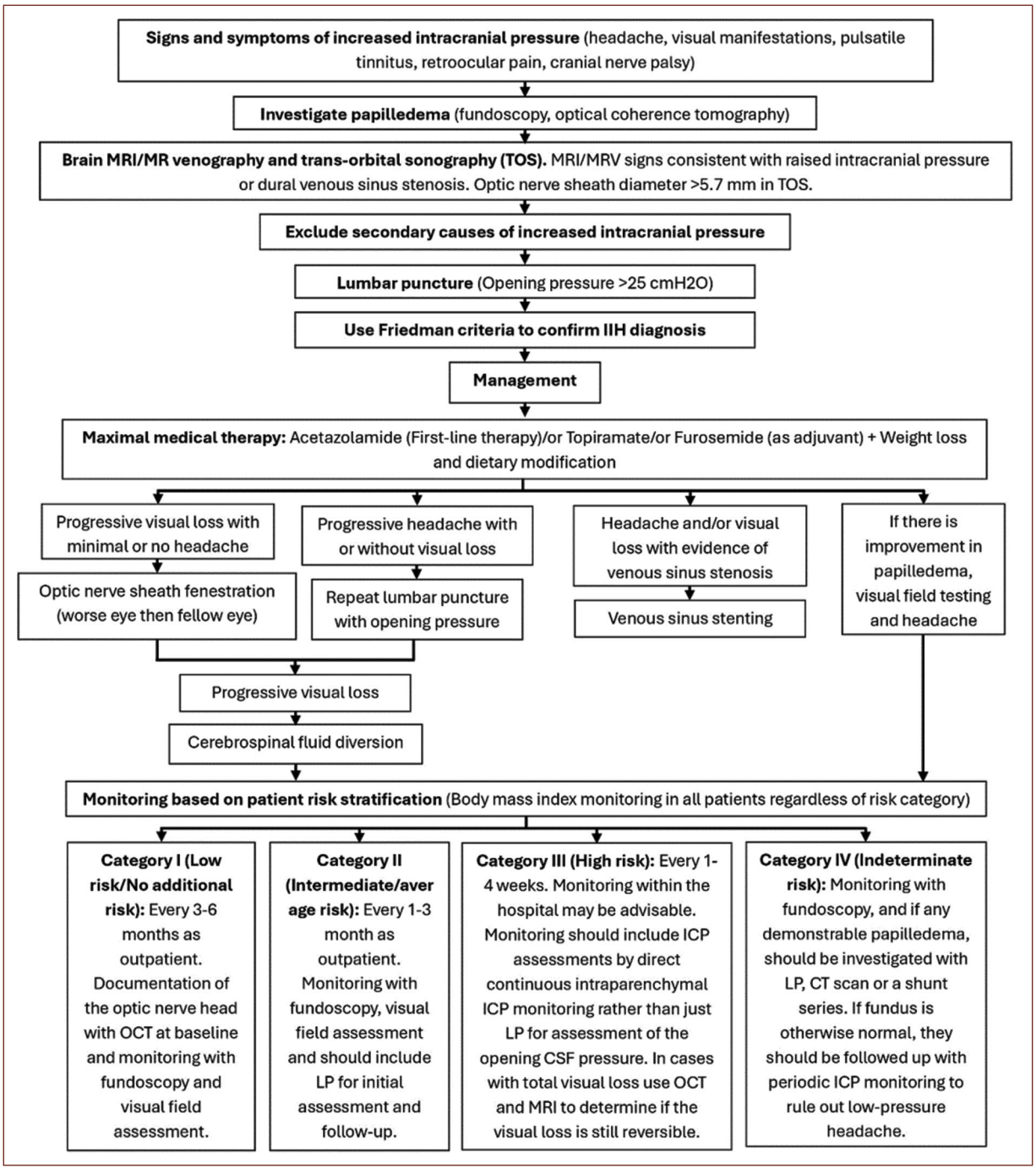

Figure 1. Diagnostic and treatment algorithm in patients with idiopathic intracranial hypertension.

after remission or surgery, should undergo fundus examination to rule out papilledema and, if absent, intermittent ICP monitoring to exclude overdrainage. Regular weight and BMI monitoring are recommended for all patients, regardless of risk category, as part of long-term management. Figure 1 presents a diagnostic and treatment algorithm for IIH.

Currently, evidence on prognosis, monitoring, and therapeutic targets in IIH remains limited. Long-term data are scarce, and standardized follow-up protocols are lacking. Future studies should include longitudinal assessments using patient-reported outcomes, OCT-based monitoring, and validated clinical scales to evaluate disease progression and treatment response.

Defining specific therapeutic goals such as stabilization of visual function, resolution of papilledema, and headache control will be crucial to optimizing management and improving long-term outcomes.

Conclusion

IIH is a disorder of unknown origin, but it is associated with obesity and abnormalities in CSF dynamics. Its impact on quality of life is significant due to persistent symptoms such as headaches, visual disturbances, and neuropsychiatric manifestations. Early diagnosis is crucial to prevent irreversible complications. Neuroimaging tools, OCT, and TOS have enhanced diagnostic accuracy, allowing for better monitoring. Treatment must be individualized, involving lifestyle changes, pharmacological therapy, and surgery in cases of refractory disease. Gaps remain in knowledge regarding follow-up approaches and risk stratification, which is why further research is necessary to optimize strategies and improve the prognosis.

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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.

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