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EDITORIAL

Integrating perspectives in contemporary neurology: from clinical observation to technological innovation

Perspectivas integradoras en la neurología contemporánea: de la observación clínica a la innovación tecnológica

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Neurology continues to evolve at an accelerated pace, shaped not only by advances in diagnostic technologies but also by a growing emphasis on patient-centered outcomes, interdisciplinary collaboration, and translational research. Contemporary neurological practice increasingly requires integrating traditional clinical observation with emerging biomarkers, rehabilitation strategies, neuropsychiatric understanding, and novel imaging modalities. The contributions gathered in this issue of Revista Mexicana de Neurociencia reflect this multidimensional evolution, illustrating how diverse lines of inquiry converge toward a more comprehensive understanding of neurological disease.

The review on quality of life in Guillain-Barré syndrome underscores how residual symptoms, fatigue, and psychosocial factors may persist despite apparent neurological recovery, reminding clinicians that functional independence does not necessarily equate to full patient well-being. Similarly, the clinical description of diabetic striatopathy reinforces the need to recognize treatable metabolic causes of movement disorders, where timely diagnosis can substantially modify prognosis. Complementing these perspectives, the study examining hematological parameters as predictors of survival in Creutzfeldt–Jakob disease explores accessible biomarkers that may inform disease trajectory in conditions where diagnostic and prognostic tools are often limited.

Rehabilitation and interdisciplinary management are also present as central themes in the current issue of the journal. The systematic review and meta-analysis evaluating immersive virtual reality therapy for Parkinson's disease exemplifies how digital technologies are increasingly incorporated into neurorehabilitation strategies. Although current evidence remains preliminary, such approaches illustrate the expanding interface between neuroscience, engineering, and clinical care, with potential implications for improving motor function, patient engagement, and long-term disease management. In parallel, the review on catatonia serves as a reminder that the boundary between neurological and psychiatric diagnosis is blurry. Greater awareness of this underrecognized neuropsychiatric syndrome can prevent diagnostic delays and improve therapeutic outcomes, emphasizing the need for clinicians to adopt integrative perspectives when evaluating complex motor and behavioral presentations.

The review of optical neuroimaging modalities for human brain mapping further represents technological innovation. Non-invasive optical techniques offer promising avenues for real-time, portable, and cost-effective

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monitoring of cerebral physiology. While still evolving, these approaches may expand access to functional neuroimaging, particularly in settings where traditional modalities remain limited. Such developments highlight how technological progress can reshape both research and clinical practice, potentially democratizing advanced neurological assessment.

Taken together, the works presented in this issue illustrate the breadth of contemporary neurology: from rare neurodegenerative diseases to metabolic movement disorders, from neuropsychiatric syndromes to rehabilitation innovation, and from clinical biomarkers to emerging neuroimaging technologies. This diversity reflects the complexity of neurological sciences, where meaningful progress often arises from interdisciplinary cooperation.

As neurological research and practice continue to advance, maintaining this integrative perspective will be essential. Improving patient outcomes requires not only diagnostic precision but also attention to quality of life, functional recovery, technological accessibility, and interdisciplinary collaboration. Therefore, Revista Mexicana de Neurociencia plays an important role in fostering this dialogue, providing a platform where clinical experience, scientific innovation, and regional perspectives converge.

The continued development of neurology in Mexico and Latin America will depend on strengthening research networks, embracing emerging technologies, and sustaining a patient-centered approach. The contributions in this issue offer valuable insights in that direction and underscore the vitality of neurological research in the region.

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ORIGINAL ARTICLE

Effect of immersive VR therapy on Parkinson's: systematic review, meta-analysis, and sequential analysis

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Abstract

Objective: *To compare the efficacy of immersive virtual reality therapy (VRT) versus conventional physical therapy (CPT) in patients with Parkinson's disease (PD) through a systematic review and meta-analysis.* **Methods:** *Systematic searches were conducted in PubMed, Web of Science, and Scopus (PRISMA 2020). We included randomized controlled trials (RCTs) comparing immersive VRT and CPT in PD patients. Primary outcomes included balance, measured with the Berg Balance Scale (BBS); functional mobility, measured with the timed "Up and Go" test (TUGT); motor performance, measured with the Unified PD Rating Scale (UPDRS) part III; and fall risk, measured with the dynamic gait index (DGI). Meta-analyses used random-effects models to compute mean differences (MD) and 95% confidence intervals. Heterogeneity (I^2), publication bias, and trial sequential analysis (TSA) were assessed.* **Results:** *Four RCTs (n = 102) were analyzed. Immersive VRT showed favorable trends, particularly for mobility (TUGT) and balance (BBS). Balance (BBS): MD = 2.26 (–1.04, 5.55), p = 0.18, I^2 = 79%; TSA showed insufficient information size (required information size = 464). TUGT: MD = 0.09 (0.00, 0.17), p = 0.04, I^2 = 0%. UPDRS III: MD = –0.19 (–3.28, 2.90), p = 0.91, I^2 = 94%. DGI: MD = 1.39 (–0.23, 3.02), p = 0.09, I^2 = 0%.* **Conclusions:** *Immersive VRT may offer functional benefits for PD, yet current evidence is insufficient to draw firm conclusions. TSA indicates a high risk of type II error. Further high-quality RCTs with standardized protocols are needed.*

Keywords: *Immersive virtual reality. Parkinson's disease. Neurorehabilitation. Randomized controlled trials. Trial sequential analysis.*

Efecto de la terapia RV inmersiva en Parkinson: revisión sistemática, metaanálisis y análisis secuencial

Resumen

Objetivo: *Comparar la eficacia de la Terapia de Realidad Virtual Inmersiva (VRT) frente a la Terapia Física Convencional (CPT) en pacientes con enfermedad de Parkinson (EP) mediante una revisión sistemática y un metaanálisis.* **Métodos:** *Se realizaron búsquedas sistemáticas en PubMed, Web of Science y Scopus (PRISMA 2020). Se incluyeron ensayos clínicos aleatorizados (ECA) que compararan terapia de realidad virtual inmersiva (VRT) con fisioterapia convencional en pacientes con enfermedad de Parkinson. Los desenlaces primarios incluyeron equilibrio medido con la Berg Balance Scale, movilidad funcional evaluada con el Timed "Up and Go" Test, desempeño motor medido con la Unified Parkinson's Disease Rating Scale parte III, y riesgo de caídas medido con el Dynamic Gait Index. Los metaanálisis utilizaron modelos de efectos*

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aleatorios para calcular las diferencias de medias (DM) e intervalos de confianza (IC) del 95%. Se evaluaron la heterogeneidad (I^2), el sesgo de publicación y el Análisis Secuencial de Ensayos (TSA). **Resultados:** *Se analizaron cuatro ECA (n = 102). La VRT inmersiva mostró tendencias favorables, especialmente en movilidad (Timed "Up and Go" Test) y equilibrio (Berg Balance Scale), pero sin diferencias estadísticamente significativas. Equilibrio (BBS): MD = 2.26 (–1.04, 5.55), p = 0.18, I^2 = 79%; el TSA mostró un tamaño de información insuficiente (RIS = 464). TUGT: MD = 0.09 (0.00, 0.17), p = 0.04, I = 0%. UPDRS III: MD = –0.19 (–3.28, 2.90), p = 0.91, I^2 = 94%. DGI: MD = 1.39 (–0.23, 3.02), p = 0.09, I^2 = 0%.* **Conclusiones:** *La VRT inmersiva podría ofrecer beneficios funcionales para la EP, aunque la evidencia actual es insuficiente para establecer conclusiones firmes. El TSA indica un alto riesgo de error tipo II. Se necesitan más ECA de alta calidad con protocolos estandarizados.*

Palabras clave: *Realidad virtual inmersiva. Enfermedad de Parkinson. Neurorrehabilitación. Ensayos controlados aleatorizados. Análisis secuencial de ensayos.*

Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative condition characterized by motor impairments such as bradykinesia, rigidity, and postural instability, significantly reducing quality of life[1]. It affects over 10 million individuals worldwide, and its prevalence continues to rise with aging populations[2,3]. Motor rehabilitation in PD plays a crucial role in preserving functional independence, reducing fall risk, and improving quality of life – particularly in stages where pharmacological treatments become less effective against symptoms such as gait disturbances, postural instability, or freezing of gait. Increasing evidence suggests that physical exercise not only alleviates motor symptoms but may also positively influence disease progression through neuroplastic and neuroprotective mechanisms[4].

Conventional physical therapy (CPT) is routinely employed to address motor deficits, but outcomes are often suboptimal or short-lived[5]. Immersive virtual reality therapy (VRT), using interactive and adaptive digital platforms, has emerged as a promising tool to stimulate neuroplasticity and enhance motor function. VRT aligns with modern approaches to personalized rehabilitation by offering multisensory feedback and task-specific training, thereby enhancing both motor learning and therapeutic engagement[5,6]. Despite this potential, randomized trials yield inconsistent results, and no meta-analytical consensus has been established[4]. This systematic review and meta-analysis aimed to compare immersive VRT with CPT on balance, mobility, motor function, and fall risk in PD. We hypothesized that VRT would provide superior motor outcomes. Trial sequential analysis (TSA) was employed to assess whether current evidence is sufficient for clinical recommendations.

Materials and methods

Search methods

This systematic review adhered to the PRISMA 2020 guidelines. The PRISMA 2020 checklist can be found in Supplementary material 1. A comprehensive search was performed in PubMed, Web of Science, and Scopus databases, with no restrictions on language or publication date. The search strategy utilized the following terms and Boolean operators: ("Parkinson's Disease" AND "Virtual Rehabilitation" OR "Virtual Reality Therapy") AND ("Randomized Controlled Trial"). The complete search process is illustrated in the PRISMA flow diagram (Fig. 1). For additional details on the full search strategy, please refer to Supplementary material 2.

Inclusion and exclusion criteria

Eligible studies were randomized controlled trials (RCTs) comparing immersive VRT with CPT in patients with a clinical diagnosis of PD. Studies had to report at least one of the following outcomes: balance (Berg Balance scale [BBS]), mobility (timed "Up" and "Go" test [TUGT]), motor performance (Unified PD Rating Scale Part III [UPDRS III]), or fall risk (dynamic gait index [DGI]). Observational studies, studies without a control group, or those lacking sufficient data to estimate effect sizes were excluded. In addition, RCTs that included video games such as Wii™ or Nintendo™ (non-immersive) were also excluded.

Data extraction information

Two independent reviewers screened titles and abstracts (FLR and BGB), followed by a full-text review to determine study eligibility. Data extraction was performed using a standardized form, collecting

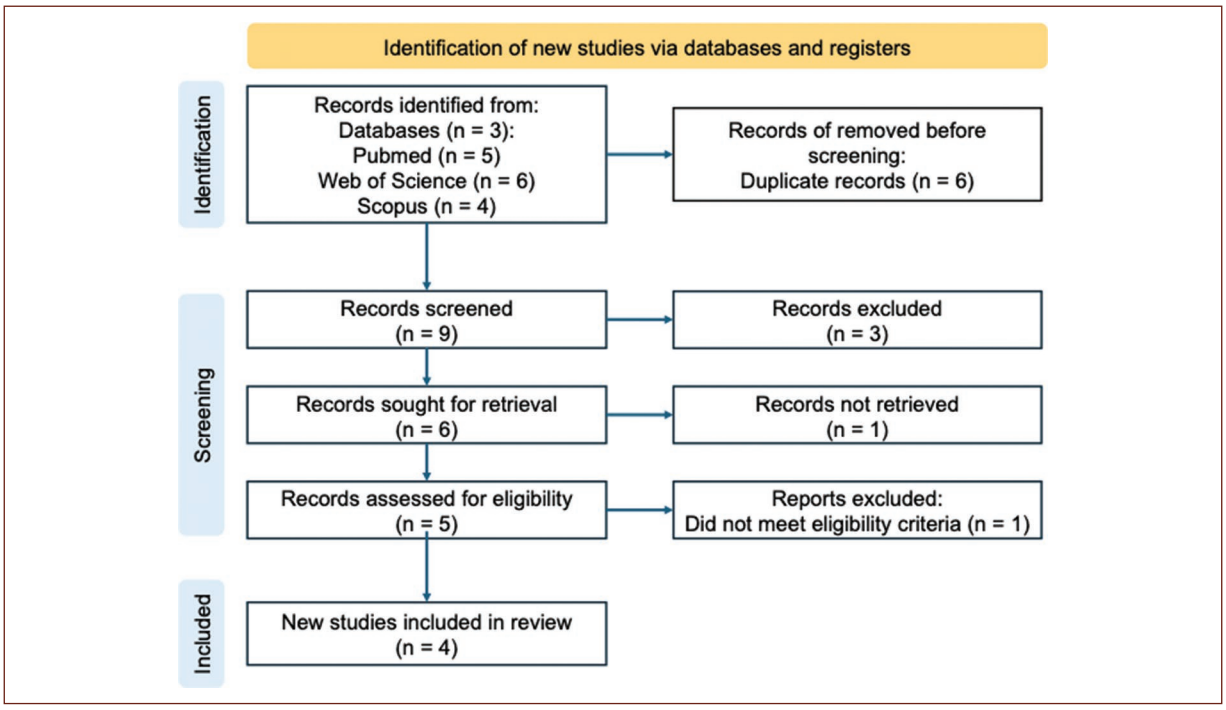

Figure 1. Prisma flowchart.

information on sample size, participant demographics (Table 1)[7-10], study design, intervention characteristics, duration, measured outcomes (Table 2)[7-10], and results included in the meta-analysis (Table 3)[7-10]. Disagreements between reviewers were resolved by consensus with an expert in movement disorders and research. Inter-rater agreement was assessed using Cohen's kappa coefficient to ensure reliability in study selection.

Quality assessment

The risk of bias for each included study was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool (Fig. 2). For additional details on the full risk of bias assessment, please refer to Supplementary Material 2. The certainty of evidence for each outcome was evaluated using the grading of recommendations, assessment, development, and evaluation methodology. Meta-analyses were conducted using Review Manager (RevMan 5.4), applying a random-effects model to calculate mean differences (MD) with 95% confidence intervals (CI) for continuous variables. Heterogeneity was quantified using the I^2 statistic. Statistical significance was set at $p < 0.05$. Random-effects models assume that true effect sizes vary across studies and are approximately normally distributed around an overall mean effect. A sensitivity analysis was planned but not conducted due to the small number of included studies (n = 4), which limited the ability to meaningfully assess robustness. Publication bias was evaluated using funnel plots and Egger's test. To assess whether the cumulative evidence was sufficient, TSA was conducted using TSA software version 0.9.5.10 β, applying a two-sided α of 5%, β of 20%, and the minimal clinically important difference (MCID) as the anticipated effect size.

Results

Search results

A total of four RCTs were included[7-10], comprising a total of 102 participants with PD. These studies directly compared the effects of immersive VRT versus CPT on motor outcomes. The selection process followed PRISMA guidelines[11] and is detailed in the flow diagram (Fig. 1).

Patient characteristics

Participants across the included studies[7-10] had a mean age of 65.4 years. They were primarily classified within stages I to IV of the Hoehn and Yahr scale,

Table 1. Population demographics

Study	Population (n)			Age mean (IQR)		Male (n)			Female (n)		
	VRT	CPT	Total	VRT	CPT	VRT	CPT	Total	VRT	CPT	Total
Feng et al.[7]	14	14	28	67.47 ± 4.79	66.43 ± 4.64	8	9	17	7	6	13
Goffredo et al.[9]	49	48	97	67.8 ± 6.6	68.2 ± 5.8	27	24	49	22	24	48
Yang et al.[8]	11	12	23	72.5 ± 8.4	75.4 ± 6.3	7	7	14	4	5	9
Pazzaglia et al.[10]	25	26	51	72 ± 7	70 ± 10	18	17	35	7	9	16

VRT: virtual reality therapy; CTP: conventional physical therapy.

Table 2. Included articles characteristics

Study	Study design	n	Participants	Intervention	Duration	Measured outcomes
Feng et al.[7]	Single-blinded RCT	28	Adults with PD based on the UK Parkinson's Disease Society Brain Bank criteria. Hoehn and Yahr score 2.5-4	Virtual reality therapy Conventional physical therapy Sessions: 45 min, once a day, 5 times a week ON medication phase: intervention 2 h after medication	12 weeks	Berg Balance Scale, Timed "Up and Go" Test, UPDRS III, functional gait assessment
Goffredo et al.[9]	Single-blinded, Multicenter RCT	97	Adults with PD based on the UK Parkinson's Disease Society Brain Bank criteria. Hoehn and Yahr score ≤ 3	Virtual reality therapy Conventional physical therapy Sessions: 45 min once a day, 3-5 times a week ON medication phase: Intervention 1 h after medication	6 to 10 weeks	Timed "Up and Go" Test, UPDRS III, miniBEST test, 6 min walking test
Yang et al.[8]	Single-blinded RCT	23	Adults with PD based on the UK Parkinson's Disease Society Brain Bank criteria. Hoehn and Yahr 2-3	Virtual reality therapy Conventional Physical Therapy Sessions: 50 min once a day, twice a week ON medication phase: intervention 1 h after medication	6 weeks	Berg Balance Scale, Timed "Up and Go" test, UPDRS III, dynamic gait index, PDQ-39
Pazzaglia et al.[10]	Single-blinded, RCT	51	Adults with PD based on the Gelb criteria	Virtual reality therapy Conventional physical therapy Sessions: 40 min once a day, 3 times a week. On the medication phase: Intervention 2 h after medication	6 weeks	Berg Balance Scale, dynamic gait index, physical composite score (SF-36), mental composite score (SF-36), disabilities of the arm, shoulder, and hand scale

RCT: randomized controlled trial; PD: Parkinson's disease.

indicating mild-to-severe disease severity. The duration of the interventions ranged between 6 and 12 weeks. Baseline demographic and clinical characteristics were generally comparable between intervention and control groups, although small sample sizes limited subgroup analyses.

Statical analysis

In terms of balance, assessed using the BBS, the pooled MD was 2.26 with a 95% CI of –1.04-5.55, which was not statistically significant (p = 0.18). Considerable heterogeneity was observed (I^2 = 79%), and

Table 3. Data included in the meta-analysis

Study	Berg balance scale				Timed "Up and Go" test				UPDRS III				Dynamic gait index			
	VRT		CTP		VRT		CTP		VRT		CTP		VRT		CTP	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Feng et al.[7]	6.07	0.35	1.93	0.7	3.29	0.94	2.71	0.97	3.64	1.25	3.36	1.93	NA	NA	NA	NA
Goffredo et al.[9]	NA	NA	NA	NA	–0.7	0.19	–0.78	0.23	–2.5	0.8	0.35	0.8	NA	NA	NA	NA
Yang et al.[8]	3.36	2.38	4.17	5.01	–3.34	3.67	–3.07	3.15	2.55	5.96	–3.17	8.73	4.09	2.98	3.17	2.86
Pazzaglia et al.[10]	3.6	2.38	0.8	7.41	NA	NA	NA	NA	NA	NA	NA	NA	1.6	4.47	–0.2	3,51

SD: standard deviation; VRT: virtual reality therapy; CTP: conventional physical therapy; NA: not available or not reported in the original publication.

Figure 2. Risk of bias summary for included randomized controlled trials. Assessed using the Cochrane Risk of Bias Tool across seven domains. Symbols indicate low risk ("+"), unclear risk ("?"), or high risk ("–").

TSA confirmed that the required information size (RIS = 464) had not been reached, suggesting insufficient power for conclusive interpretation (Figs. 3 and 4). For functional mobility, evaluated with the TUGT, the pooled MD was 0.09 (0.00, 0.17), achieving statistical significance (p = 0.04) with no heterogeneity (I^2 = 0%) (Fig. 5). The TUGT is a widely used clinical measure that assesses the time it takes for an individual to stand up from a chair, walk a short distance, turn, return, and sit down. It reflects functional mobility, which is critical for daily activities and fall prevention. In PD, impaired TUGT performance is strongly associated with higher fall risk and reduced independence, making even modest improvements potentially meaningful in clinical contexts. Regarding motor performance, as measured by the Unified PD Rating Scale Part III (UPDRS III), no significant difference was found between groups (MD = –0.19 [-3.28, 2.90], p = 0.91), with high heterogeneity (I^2 = 94%) (Fig. 6). Considerable heterogeneity was observed (I^2 = 79%). A subgroup analysis was

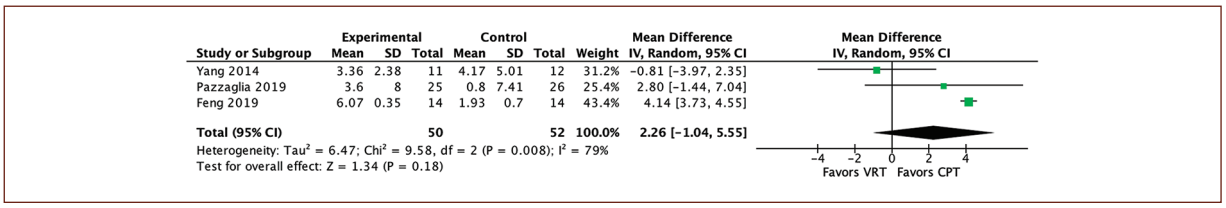

Figure 3. Forest plot of studies evaluating the effect of Virtual Reality Therapy (VRT) on balance using the Berg Balance Scale (BBS), compared to conventional physical therapy (CPT). The pooled mean difference was 2.26 [–1.04, 5.55], with no statistical significance (p = 0.18) and high heterogeneity (I^2 = 79%).

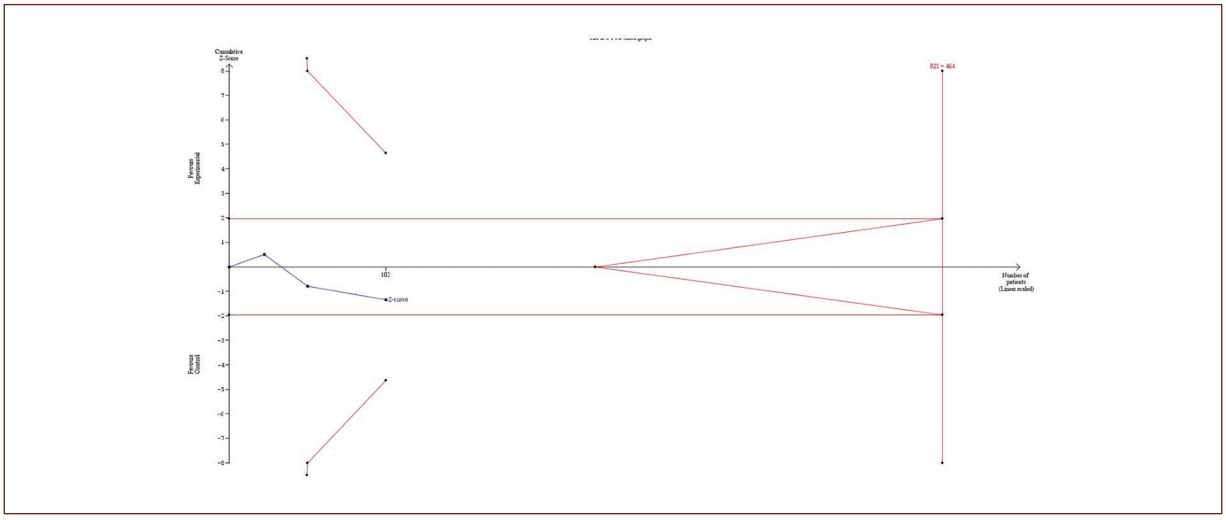

Figure 4. Trial Sequential Analysis (TSA) for the effect of Virtual Reality Therapy (VRT) on balance. The cumulative Z-curve did not cross any monitoring boundaries, and the required information size (RIS = 464 patients) was not reached, indicating that current evidence is insufficient to draw firm conclusions.

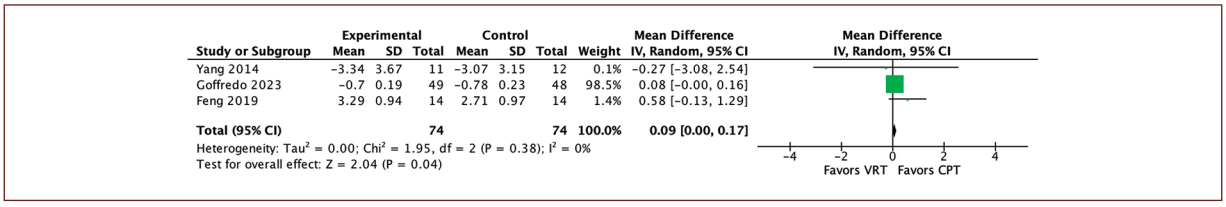

Figure 5. Forest plot of studies evaluating the effect of Virtual Reality Therapy (VRT) on functional mobility using the Timed Up and Go (TUG) test, compared to conventional physical therapy (CPT). The pooled mean difference was 0.09 [0.00, 0.17], with marginal statistical significance (p = 0.04) and no heterogeneity (I^2 = 0%).

performed to explore the sources of heterogeneity, suggesting that studies such as Feng 2019 in the BBS analysis and Yang 2014 in UPDRS III contributed substantially due to their extreme effect sizes. This variability likely stems from differences in intervention duration and the inclusion of patients at different stages of PD, which can influence responsiveness to therapy and lead to divergent outcomes. Finally, fall risk, assessed using the DGI, showed a non-significant trend favoring immersive VRT (MD = 1.39 [–0.23, 3.02], p = 0.09) with no observed heterogeneity (I^2 = 0%) (Fig. 7). No publication bias was detected upon funnel plot inspection and Egger's test. In general, the results suggest a modest but consistent

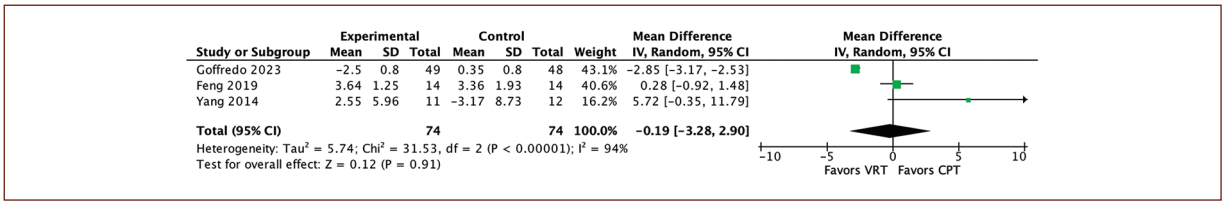

Figure 6. Forest plot of studies evaluating the effect of Virtual Reality Therapy (VRT) on motor performance using the Unified Parkinson's Disease Rating Scale Part 3 (UPDRS-III), compared to conventional physical therapy (CPT). The pooled mean difference was –0.19 [–3.28, 2.90], with no statistical significance (p = 0.91) and high heterogeneity (I^2 = 94%).

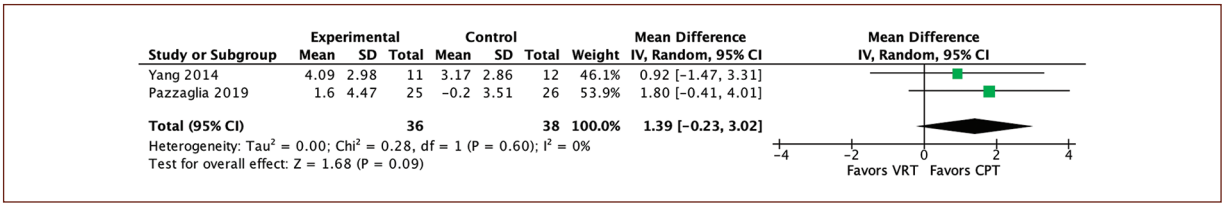

Figure 7. Forest plot of studies evaluating the effect of Virtual Reality Therapy (VRT) on fall risk, measured using the Dynamic Gait Index (DGI), compared to conventional physical therapy (CPT). A trend favoring VRT was observed (MD = 1.39 [–0.23, 3.02]), though it did not reach statistical significance (p = 0.09) and showed no heterogeneity (I^2 = 0%).

trend in favor of immersive VRT; however, the current body of evidence is underpowered and limited by statistical and clinical heterogeneity.

Discussion

This meta-analysis assessed the comparative efficacy of immersive VRT and CPT in PD motor rehabilitation. Although trends favored immersive VRT, only mobility (TUGT) reached statistical significance, and even then, the effect was marginal. Balance improved modestly with immersive VRT, but did not surpass the MCID of ~4 points on BBS. High heterogeneity in BBS and UPDRS III suggests protocol and population variability across studies. Mobility improvements were consistent and may reflect the motivational and task-specific nature of immersive VRT. Fall risk and motor scores did not show meaningful changes, possibly due to limited intervention duration or insufficient power. TSA confirmed the current sample size is underpowered, particularly for balance-related outcomes (Fig. 4). By assessing whether the accrued information is sufficient to draw firm conclusions, TSA helps prevent premature claims of benefit or lack of effect based on underpowered data. The finding that the Z-curve did not cross significance boundaries and that the RIS was not reached underscores the need for larger, well-designed trials to determine the true clinical impact of immersive VRT in PD rehabilitation.

Our findings align with previous narrative reviews suggesting the potential of immersive VRT[12-24] but insufficient high-quality evidence for routine implementation. Although several published meta-analyses have reported positive outcomes for VRT in PD[12,13,15-18,19,21,22], many of these include RCTs that rely on commercial video game systems such as Nintendo Wii™ (non-immersive). This methodological choice introduces a significant limitation, as these systems are not designed for therapeutic use and lack clinical calibration, reducing the reliability and translatability of the findings to real-world rehabilitation settings[25,26].

It is critical to differentiate clinically validated immersive VRT from entertainment-based gaming platforms. Immersive VRT is specifically developed for medical purposes, employing task-specific training, motion tracking, and customizable feedback to target motor deficits under professional supervision[26]. In contrast, devices such as the Wii™ or Nintendo™ consoles offer generic, non-adaptive experiences without therapeutic frameworks, progression protocols, or outcome standardization[26]. Their use may enhance patient engagement superficially, but it does not fulfill the principles of evidence-based rehabilitation[25,26]. Therefore, RCTs incorporating such systems were deliberately excluded from the present meta-analysis. Including

them would compromise the methodological rigor and distort the clinical relevance of the conclusions, given the fundamental differences in design, intensity, and neurorehabilitative value between commercial gaming and structured immersive VRT.

Immersive VRT should not be viewed as a replacement, but rather as an evolution of traditional rehabilitation paradigms. Its integration into clinical practice holds the potential to deliver structured, adaptive training protocols that respond to individual motor phenotypes, disease stage, and symptom dynamics. Investigating its efficacy through well-designed RCTs is therefore not only an important methodological consideration but also a fundamental step toward precision medicine in PD rehabilitation.

Limitations include the small overall sample size, variability in intervention protocols and duration, and lack of long-term follow-up data. In addition, the included RCTs enrolled participants at different stages of PD (Hoehn and Yahr scores), introducing potential selection bias and heterogeneity in baseline characteristics that could influence treatment response. The risk of type II error also remains due to underpowered analyses in some outcomes. Future research should prioritize multicenter RCTs with standardized immersive VRT protocols, well-defined and robust control groups, and extended follow-up periods to assess the sustainability of effects. Economic evaluations and studies examining adherence and accessibility in diverse settings are also warranted to support implementation in clinical practice.

Conclusion

This meta-analysis demonstrates trends suggesting possible benefits in mobility, though not in balance or overall motor severity. These findings highlight the potential role of immersive VRT as an adjunct in PD rehabilitation, while underscoring the need for larger, well-designed trials to confirm its clinical effectiveness across different motor domains.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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

Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.25000019. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Diabetic striatopathy in Hispanic patients: recognizing a variable yet treatable movement disorder

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Abstract

Objective: *To describe clinical features, diagnostic challenges, and therapeutic response of diabetic striatopathy in Latin American patients, an underrepresented population in current literature, and to highlight the importance of early recognition and interdisciplinary collaboration in improving diagnosis and management.* **Methods:** *Case series of two Latin American women with poorly controlled type 2 diabetes mellitus who developed hyperkinetic movement disorders. Clinical presentation, neuroimaging findings, diagnostic approach, and clinical outcomes following metabolic and symptomatic treatment were analyzed.* **Results:** *One patient presented with acute-onset chorea accompanied by pain and hypoesthesia, with striatal hyperdensity on computed tomography and T1 hyperintensity on magnetic resonance imaging, achieving complete symptom resolution within 48 hours after intensive insulin therapy. The second patient developed progressive choreiform movements, initially misdiagnosed as epilepsy, without response to antiepileptic drugs. Neuroimaging confirmed diabetic striatopathy; insulin therapy produced partial improvement, and adjunctive haloperidol reduced movement severity, with residual symptoms at discharge. Both cases demonstrated characteristic imaging findings despite distinct clinical phenotypes.* **Conclusions:** *Diabetic striatopathy shows heterogeneous clinical presentations and may mimic other neurological disorders, leading to diagnostic delays. Early recognition and prompt glycemic control are essential, although treatment response varies and may require individualized management strategies.*

Keywords: *Diabetes. Hyperglycemia. Chorea. Basal ganglia. Case report.*

Estriatopatía diabética en pacientes hispanos: reconociendo un trastorno del movimiento variable pero tratable

Resumen

Objetivo: *Describir las características clínicas, los desafíos diagnósticos y la respuesta terapéutica de la estriatopatía diabética en pacientes latinoamericanos, una población escasamente representada en la literatura, y resaltar la necesidad de reconocimiento clínico temprano y colaboración interdisciplinaria.* **Métodos:** *Serie de casos de dos mujeres latinoamericanas con diabetes mellitus tipo 2 mal controlada que desarrollaron trastornos del movimiento hipercinéticos. Se analizaron las manifestaciones clínicas, hallazgos de neuroimagen, abordaje diagnóstico y evolución clínica tras tratamiento metabólico y sintomático.* **Resultados:** *Una paciente presentó corea de inicio agudo asociada a dolor e hipoestesia, con hiperdensidad estriatal en tomografía e hiperintensidad en T1 en resonancia magnética, logrando resolución completa tras control glucé-*

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mico intensivo con insulina en 48 horas. La segunda paciente desarrolló movimientos coreiformes progresivos, inicialmente diagnosticados como epilepsia, sin respuesta a antiepilépticos. La neuroimagen confirmó estriatopatía diabética; el tratamiento con insulina produjo mejoría parcial y la adición de haloperidol redujo la severidad de los movimientos, persistiendo síntomas residuales. Ambos casos mostraron hallazgos radiológicos característicos pese a fenotipos clínicos distintos. **Conclusiones:** *La estriatopatía diabética presenta manifestaciones clínicas heterogéneas y puede simular otras enfermedades neurológicas, favoreciendo retrasos diagnósticos. El reconocimiento temprano y el control glucémico oportuno son fundamentales, aunque la respuesta terapéutica puede variar y requerir manejo individualizado.*

Palabras clave: *Diabetes. Hiperglucemia. Corea. Ganglios basales. Reporte de caso.*

Introduction

Diabetic striatopathy (DS) is a rare neurological complication associated with poorly controlled Type 2 diabetes (T2D). It is characterized by non-ketotic hyperglycemia, hyperdensity of the basal ganglia on computed tomography (CT), and contralateral choreiform movements. While predominantly reported in elderly Asian females, cases in Latin American populations remain underrepresented, limiting understanding of potential ethnic variations in presentation and management[1-3].

The term DS is relatively recent and corresponds to previously used diagnostic labels such as hyperglycemia-associated chorea, chorea hyperglycemia basal ganglia syndrome (CHBG), and non-ketotic hyperglycemic hemichorea. Including these synonymous terms helps prevent diagnostic and terminological confusion in the literature. In this manuscript, the term Latin American is used instead of Hispanic to more precisely describe individuals originating from Spanish-speaking countries in Latin America. Unlike the broader term Hispanic, which may include people from Spain or Spanish-speaking populations in the United States, Latin American specifically refers to individuals from Mexico, Central America, South America, and the Spanish-speaking Caribbean, which aligns with the origin of the patients presented in this case series.

A previous prospective series by Cervantes-Arriaga et al., reported 10 Mexican patients with hyperglycemia-associated movement disorders and described similar clinical and neuroimaging features[4]. However, that study predated the widespread adoption of the term “diabetic striatopathy” and used earlier nomenclature. Our report adds to this limited but growing body of literature by applying current diagnostic terminology and focusing specifically on clinical variability, diagnostic challenges, and treatment response in Latin American patients.

This case report was prepared in accordance with the CARE (CAse REport) guidelines to ensure completeness, transparency, and accuracy in reporting.

Clinically, DS presents as an acute or subacute hyperkinetic movement disorder, frequently misdiagnosed as stroke, epilepsy, or structural lesions of the basal ganglia. Involuntary movements, predominantly chorea or ballism, typically affect one side of the body. Choreic movements are irregular, non-repetitive, and random, while ballistic movements are more forceful and wide-amplitude. These abnormal movements are often exacerbated by voluntary activity and tend to resolve during sleep[5-9].

Several pathophysiological mechanisms have been proposed to explain the clinical manifestations. One prevailing theory suggests that non-ketotic hyperglycemia depletes gamma-aminobutyric acid (GABA) levels, leading to reduced acetylcholine and resulting in basal ganglia dysfunction and chorea. Another theory implicates ischemic injury to the basal ganglia in the context of uncontrolled diabetes as the underlying cause. In addition, neurodegeneration due to hyperosmolarity has been proposed as a plausible mechanism. The presence of gemistocytes-swollen reactive astrocytes observed following ischemic injury, may contribute to the T1 hyperintensity on MRI, potentially integrating elements from the aforementioned theories[2,3,10,11].

Average blood glucose and glycated hemoglobin (HbA1c) levels in DS patients tend to be markedly elevated (414-481.5 mg/dL and 13.1-14.4%, respectively), underscoring the association with hyperglycemia. While DS is predominantly linked to non-ketotic hyperglycemia, 81.7% of patients in one study exhibited no evidence of ketosis, it has also been reported in patients with diabetic ketoacidosis and other ketotic states[3,12-16].

Neuroimaging plays a critical role in diagnosis. CT scans often reveal unilateral hyperdensity in the striatum contralateral to the side affected by involuntary movements. Magnetic resonance imaging (MRI), particularly T1-weighted sequences, is more sensitive and

typically shows characteristic striatal hyperintensity without mass effect and with preservation of the internal capsule[17-20].

Prompt glycemic control with insulin remains the cornerstone of treatment. However, in some cases, adjunctive therapy with antichoreic agents may be required. Clinical resolution can occur within 2-14 days with glycemic correction and symptomatic treatment. Symptom resolution through glycemic control alone occurs in only 25% of patients, while the addition of antichoreic agents increases the response rate to approximately 76%[3,9,12,21].

Resolution of radiological abnormalities often lags behind clinical improvement, with a median duration of 60 days for CT findings and up to 180 days for MRI. Approximately 20% of patients experience recurrence of abnormal movements even after initial radiological resolution, emphasizing the importance of ongoing clinical and imaging follow-up[1,3,12].

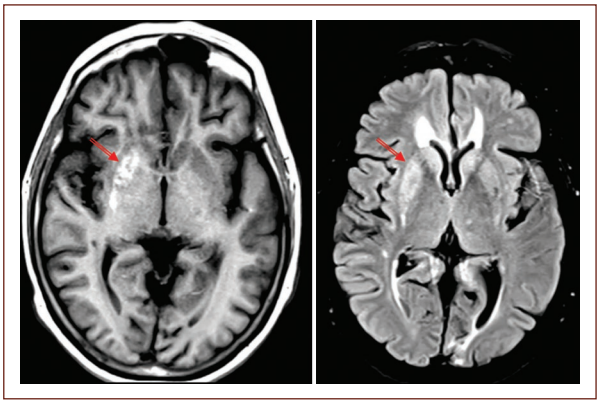

Figure 1. Axial T1-weighted and fluid-attenuated inversion recovery magnetic resonance imaging of case 1 demonstrating a hyperintense lesion in the right striatum (arrow), consistent with diabetic striatopathy.

Case presentation

Case 1

A 62-year-old Latin American woman with a history of long-standing T2D and hypertension presented with an acute-onset hyperkinetic movement disorder affecting her left upper limb. The involuntary movements, described as continuous, non-rhythmic, and multidirectional, began insidiously during the night and progressively worsened over 4 days, prompting medical evaluation. The patient also reported pain and hypoesthesia in the affected limb and ipsilateral facial region.

She denied any prior history of movement disorders, epilepsy, or stroke, as well as any family history of neurological conditions. Her glycemic control had been consistently poor, with blood glucose levels persistently exceeding 300 mg/dL. Her current pharmacological treatment included Losartan for hypertension, with no recent modifications in medication use or evidence of intercurrent infections.

Neurological examination revealed choreiform movements predominantly affecting the left hand, with mild involvement of the proximal upper limb and ipsilateral face. The movements were involuntary, continuous, and exacerbated by voluntary action and distraction maneuvers, while subsiding at rest. The remainder of the neurological and systemic examination was unremarkable, with no cognitive impairment, motor weakness, or pyramidal signs.

On admission, her blood glucose level was 331 mg/dL (reference range 7-100 mg/dL), and laboratory workup, including venous blood gas, renal function panel, complete blood count, and serum electrolytes, was within normal limits. Non-contrast brain CT revealed a subtle hyperdensity in the right striatum, without associated mass effect or hemorrhagic transformation. MRI demonstrated a T1-weighted hyperintense lesion in the right striatum, with corresponding hypointensity on T2 and fluid-attenuated inversion recovery sequences (Fig. 1), consistent with DS. No additional structural, metabolic, or vascular abnormalities were identified.

A diagnosis of DS was established. Intensive glycemic control with insulin therapy was initiated, achieving a reduction in blood glucose levels to < 100 mg/dL within 48 h. The choreiform movements resolved completely, along with the associated pain and sensory disturbances. The patient was discharged 48 h after admission, entirely asymptomatic, with no residual neurological deficits.

Case 2

A 70-year-old Latin American woman with a history of poorly controlled T2D presented to the emergency department with recurrent, episodic involuntary movements affecting her right hemibody. She reported a 6-month history of progressive hyperkinetic episodes, which had initially been intermittent and brief (lasting seconds to minutes) but had become continuous over time. A previous misdiagnosis of epilepsy had led to treatment with phenytoin, with no clinical benefit.

She denied a history of stroke, traumatic brain injury, or neurodegenerative disorders, and there was no

family history of movement disorders. Her diabetes had been poorly controlled, with erratic glucose monitoring and lack of adherence to prescribed treatment.

On neurological examination, the patient exhibited non-rhythmic, dance-like choreiform movements, predominantly affecting the proximal right upper and lower limbs. The movements were present at rest, exacerbated by voluntary action, and significantly interfered with daily activities, including walking and feeding. Importantly, they did not occur during sleep, and no myoclonus, dystonia, or pyramidal signs were noted. The rest of the neurological and systemic examination was unremarkable.

Initial laboratory investigations revealed severe hyperglycemia of 469 mg/dL (reference range 70-100mg/dL), with HbA1c levels consistent with chronic poor glycemic control. Complete blood count, renal function panel, serum electrolytes, venous blood gas analysis, and ketone bodies were within normal limits. Brain CT demonstrated a hyperdense lesion in the left basal ganglia, with no associated hemorrhage or ischemic infarct (Fig. 2). Based on these findings, DS was diagnosed.

Intravenous insulin therapy was promptly initiated, leading to partial glycemic control. Given the persistence of disabling choreiform movements, haloperidol (5 mg twice daily) was introduced as adjunctive therapy. After 3 days of treatment, the severity and frequency of the involuntary movements improved partially, but mild residual symptoms persisted at discharge.

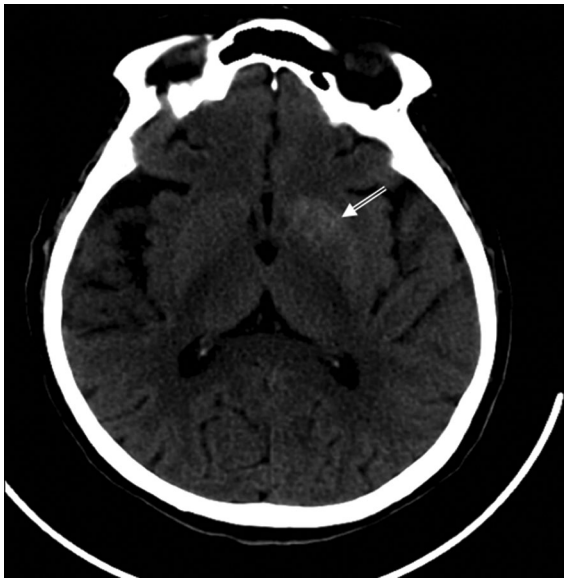

Figure 2. Non-contrast computed tomography of case 2 showing a hyperdense lesion in the left basal ganglia (arrow), a characteristic finding in diabetic striatopathy.

Discussion

This case series highlights the heterogeneous clinical presentation of DS and underscores the importance of early recognition and accurate diagnosis, particularly in underrepresented populations. A prior case series conducted in Mexico by Cervantes-Arriaga et al., described 10 patients with hyperglycemia-associated movement disorders exhibiting similar neuroimaging and clinical features, although the term “diabetic striatopathy” was not yet in use. This supports the presence of this clinical entity in Latin American populations and reinforces the importance of recognizing it under its current diagnostic framework[1,2,4].

DS presents with variable phenotypes, ranging from acute-onset continuous movements with sensory symptoms (Case 1) to progressive episodic choreiform movements (Case 2). The diagnostic delay in Case 2, initially labeled as epilepsy, underscores a recurrent issue in DS: its mimicry of other neurological conditions, particularly stroke, seizure disorders, or functional movement disorders. These diagnostic pitfalls can lead to ineffective or inappropriate treatment, delaying targeted interventions such as glycemic correction or dopamine antagonism[3,5,11,12]. Our findings reinforce the need for heightened clinical suspicion in patients with poorly controlled diabetes and movement disorders[6].

Neuroimaging continues to be pivotal in diagnosis, as both cases showed striatal hyperdensity on CT and characteristic T1 hyperintensity on MRI. These findings support the role of neuroimaging not only in excluding structural lesions but also in confirming DS in the appropriate clinical context. Interestingly, the radiological features in our patients were subtle, highlighting the importance of clinician awareness in interpreting these findings when DS is suspected[6,12,19,20].

Pathophysiologically, both cases reinforce the notion that DS may not be exclusively related to non-ketotic hyperglycemia. One patient exhibited a clinical profile consistent with prolonged metabolic dysregulation and required antichoreic therapy, suggesting a possible cumulative or neurotoxic mechanism. The variation in treatment response aligns with the theory that striatal injury in DS may result from a combination of factors, including ischemia, astrocytic swelling (gemistocyte

Table 1. Comparative summary of diabetic striatopathy case series reported in the literature

Authors	Year	Country	Sample size	Mean age (years)	F:M	Glc mg/dL	Choreic/ballistic (%)
Oh et al.[6]	1990-2001	South Korea	53	71	1:0.57	481.5	90.57
Chua et al.[8]	1992-2018	China	176	67.6	1:1.7	414	88
Aras et al.[7]	2018-2021	Turkey	19	72.2	1:0.19	649	68.4
Dubey et al.[16]	2014-2021	India	59	55.4	1:1.1	419	69.5
Cervantes et al.[5]	2011	Mexico	10	67.7	7:3	359.7	100
Ours	2023-2024	México	2	66	-	400	100

Data include study authors, publication period, country, sample size, mean age, female-to-male ratio (F:M), mean plasma glucose levels (mg/dL), and the percentage of patients presenting with choreic or ballistic movements.
Glc: glucose; F:M: female-to-male ratio. Data were extracted from the cited references.

accumulation), and neurotransmitter depletion (e.g., GABA and acetylcholine), rather than a single metabolic insult[2,3,11,12].

A comparison of DS cases across different populations (Table 1) reveals key epidemiological and clinical differences. The mean age of presentation in our patients (66 years) is comparable to cohorts from South Korea (71 years), China (67.6 years), and Turkey (72.2 years) but is notably higher than in India (55.4 years)[6,17]. This may reflect regional or genetic factors influencing disease onset. Glucose levels (400 mg/dL) in our cases were within the reported range but lower than in Turkey (649 mg/dL), suggesting that hyperglycemia alone may not fully account for DS pathogenesis[3].

Interestingly, our patients exhibited 100% choreiform/ballistic movements, consistent with findings from another Latin American series by Cervantes-Arriaga et al., in which all 10 patients also presented hyperkinetic motor phenotypes. This contrasts with the 68.4-90.57% choreiform presentation rates reported in non-Latin American cohorts[6-8,17]. This observation raises the possibility that ethnic, genetic, or metabolic factors may influence the motor phenotype of DS. In addition, while a female predominance is well-documented in DS, the small sample size in our cohort precluded sex-based comparisons[3,18].

Case 1 responded rapidly to insulin alone, while Case 2 required adjunctive haloperidol, aligning with reports that glycemic control alone resolves symptoms in ~25% of cases, whereas dopamine receptor antagonists increase resolution rates to ~76%[12]. The differing responses suggest variability in underlying mechanisms, ranging from acute metabolic dysfunction to chronic neurotoxicity or vascular injury[2,12].

Our findings highlight the need for expanded research in Latin American populations to assess whether these age, metabolic, and clinical differences hold statistical and clinical significance[3,9]. Future studies should focus on long-term outcomes, genetic predisposition, and neuroimaging evolution to refine diagnostic and therapeutic approaches for DS[2,9].

Several limitations must be acknowledged. First, this is a small case series, limiting the generalizability of findings to the broader Latin American population. Second, the lack of long-term follow-up prevents assessment of potential symptom recurrence or neuroimaging evolution over time. Finally, while neuroimaging was essential for diagnosis, more detailed pathophysiological analyses (e.g., metabolic imaging or histopathological correlation) were not performed[5].

Conclusion

DS should be a key differential diagnosis in patients presenting with acute hyperkinetic movement disorders and poorly controlled diabetes, particularly in populations where it remains underrecognized. Early diagnosis and glycemic management are essential for optimal outcomes, but therapeutic response varies, warranting further investigation into predictors of treatment success. Expanding research in Latin American populations will provide crucial insights into the epidemiology, pathogenesis, and tailored management of this rare but clinically significant diabetic complication.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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

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ORIGINAL ARTICLE

Hematologic data predict survival in Mexican Mestizo people with Creutzfeldt-Jakob disease

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Abstract

Objective: *Creutzfeldt-Jakob disease (CJD) is a rare cause of rapidly progressive dementia due to the accumulation of misfolded prion proteins (PrPC) in the brain. Mortality is essentially universal within months to a few years after symptom onset. Here, we evaluated biomarkers derived from baseline complete blood counts (CBCs) in search of readily available predictors of disease progression using survival span as an outcome.* **Methods:** *We analyzed retrospective data derived from the baseline CBC from Mexican Mestizo individuals. We performed Spearman rho correlation to determine the association between survival time from disease onset with leukocyte and erythrocyte counts of people with CJD. We used Cox proportional hazard models to predict survival time, and log-rank tests to compare survival of subgroups.* **Results:** *We included 22 people with probable or definite CJD. Twelve (55%) were female. The mean age at diagnosis was 55 years (interquartile range: 25–85). Lower hemoglobin ($r = –0.494$, $p = 0.019$), hematocrit ($r = –0.445$, $p = 0.037$), and lymphocyte ($r = –0.421$, $p = 0.050$; log-rank test: $\chi^2 = 3.7$, $p = 0.05$) counts and higher neutrophils ($r = 0.404$, $p = 0.061$; log-rank test: $\chi^2 = 5.7$, $p = 0.02$) were associated with longer survival time.* **Conclusions:** *In the present study, we observed that common hematological values derived from a CBC were associated with survival span in people living with CJD. Those values support previous observations suggesting that the circulating availability of wild-type prion protein in blood cells is a limiting factor in the production of misfolded prion protein.*

Keywords: *Creutzfeldt-Jakob disease. Complete blood counts. Prion disease. Survival time. Biomarkers.*

Los datos hematológicos predicen la supervivencia en mestizos mexicanos con enfermedad de Creutzfeldt-Jakob

Resumen

Objetivo: *La enfermedad de Creutzfeldt-Jakob (ECJ) es una causa de demencia de rápida progresión debido a la acumulación de proteínas priónicas cerebrlaes mal plegadas. La mortalidad es prácticamente universal en un plazo de meses a pocos años tras el inicio de los síntomas. En este estudio evaluamos biomarcadores derivados de la biometría hemática (BH) basal buscando de predictores accesibles de progresión de ECJ, utilizando la supervivencia como desenlace.* **Métodos:** *Analizamos datos retrospectivos derivados de BH basal de individuos mestizos mexicanos con ECJ. Realizamos*

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una correlación rho de Spearman para determinar la asociación entre la supervivencia desde el inicio de síntomas y los recuentos de leucocitos y eritrocitos. Utilizamos modelos de riesgos proporcionales de Cox para predecir el tiempo de supervivencia y pruebas de log-rank para comparar la supervivencia de los subgrupos. **Resultados:** *Incluimos a 22 personas con ECJ probable o confirmada. Doce (55%) eran mujeres. La edad media al momento del diagnóstico fue de 55 años (RIC: 25-85). Un recuento bajo de hemoglobina (r = –0.494, p = 0.019), hematocrito (r = –0.445, p = 0.037) y linfocitos (r = –0.421, p = 0.050; prueba log-rank: χ^2 = 3.7, p = 0.05) y un recuento elevado de neutrófilos (r = 0.404, p = 0.061; prueba log-rank: χ^2 = 5.7, p = 0.02) se asociaron con una mayor supervivencia.* **Conclusiones:** *En el presente estudio observamos que los valores hematológicos comunes obtenidos a partir de la BH se asociaron con la supervivencia en personas con ECJ. Estos valores respaldan observaciones previas que sugieren que la disponibilidad circulante de la proteína priónica silvestre en las células sanguíneas puede ser un factor limitante en la producción de proteínas priónicas mal plegadas.*

Palabras clave: *Enfermedad de Creutzfeldt-Jakob. Hemograma completo. Enfermedad priónica. Tiempo de supervivencia. Biomarcadores.*

Introduction

Creutzfeldt-Jakob disease (CJD) is a rare pathology caused by misfolded (PrPSc) prion protein (PrPC), characterized by rapidly progressive dementia[1,2]. The median survival in white and Asian populations is about 1 year from the onset of symptoms[1,3,4]. A longer survival than the above-mentioned has been reported in people of Mexican ancestry[5]. A series of studies facilitate the diagnosis and progression of CJD; however, in low-and middle-income countries, most are not readily available[2,4]. The identification of low-cost, ubiquitous laboratory markers of disease progression is crucial. Here, we analyzed the correlation between biomarkers derived from the complete blood count (CBC), a readily available test, with survival rates in people with CJD in Mexico.

Materials and methods

We conducted an observational, cross-sectional study based on retrospectively collected data. For research purposes, dates were accessed in DD/MM/YYYY format. We reviewed data from a cohort of previously unpublished cases of CJD from two tertiary-care public institutions in Mexico City: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, between January 1, 1990, and July 31, 2024. Inclusion criteria were all records obtained that had a diagnosis of probable CJD (1) rapidly progressive dementia; (2) the presence of at least two of the following: akinetic mutism, myoclonus, pyramidal or extrapyramidal signs, visual or cerebellar dysfunction; (3) 14-3-3 protein positivity; or (4) pathological electroencephalogram or pathological magnetic resonance imaging)] or definitive (genetically confirmed)[6]; likewise, complete clinical and paraclinical data were available, as well as accurate information on their evolution, and their follow-up had ended due to death or discharge from the institution. Exclusion criteria were those patients with a diagnosis of rapidly progressive dementia who did not meet sufficient criteria for a probable or definitive diagnosis of CJD, as well as those patients with a diagnosis of possible CJD[6]. Survival time was defined as the time elapsed from the onset of the first symptom (as defined above) to death or the last live report of the patient. For our objectives, as a baseline, we used the first blood sample collected after the onset of symptoms. Continuous variables are presented as median and interquartile range (IQR). Spearman's rho correlation analysis was performed to determine the associations between survival time and leukocyte and erythrocyte counts. All leukocyte and erythrocyte indices analyzed were binned in the median. Cox proportional hazard models were used to predict survival time, log-rank tests were applied to compare the survival of groups with low and high cell counts with respect to their medians. All statistical analyses were performed using R software, v. 4.3.2[7]. To minimize the risk of Type I error derived from the simultaneous analysis of multiple hematologic indices, we applied multiple comparison correction methods using the Bonferroni, Holm, and Benjamini-Hochberg procedures (data not shown). This study protocol was reviewed and approved by the Ethics in Research and Human Research Committees of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, with approval number ID: NER-5277-24-26-1. Due to the retrospective nature of the study, a waiver for informed consent was granted.

Results

We analyzed baseline hematologic data from 22 people with probable or confirmed CJD; 12 (55%) were

Table 1. Leukocyte and erythrocyte indices from people with CJD in Mexico

Leukocyte/erythrocyte index	Sample, total n	Median	IQR	Range	Correlation with survival time, r	p
Leukocytes (K/uL)	22	8.35	6.44-9.40	2.88-14.50	–0.051	0.819
Erythrocytes (M/uL)	22	4.87	4.56-5.29	3.29-8.70	–0.073	0.743
Hemoglobin (g/dL)	22	14.85	13.05-15.75	10.40-17.60	–0.494	0.019
Hematocrit (%)	22	44.80	39.65-46.75	30.00-50.50	–0.445	0.037
MCV (fL)	22	90.25	88.02-92.42	61.00-97.60	+0.197	0.378
MCH (pg)	22	30.25	30.00-31.25	25.90-34.30	+0.096	0.670
MCHC (%)	22	33.60	33.00-34.37	28.70-36.70	–0.073	0.746
Platelets (K/uL)	22	250.50	183.25-302.00	107.00-406.00	+0.311	0.158
Lymphocytes (%)	22	22.55	15.45-33.42	4.00-53.40	–0.421	0.050
Monocytes (%)	22	8.75	6.37-9.57	2.50-13.80	–0.221	0.320
Neutrophils (%)	22	68.80	52.77-75.00	29.40-86.90	+0.404	0.061
Eosinophils (%)	22	1.75	1.35-2.62	0.40-9.70	–0.050	0.823
Basophiles (%)	22	0.45	0.40-0.70	0-1.20	+0.053	0.811

MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration, CJD: Creutzfeldt-Jakob disease.

female. One subject was categorized as definite CJD, confirmed genetically, while 21 people met the criteria for probable CJD. The mean age at diagnosis was 55 years (IQR: 25-85, median: 59 years). The median survival of the cohort was 187 days. The mean survival of the cohort was 257 days. One-year survival rate was 32% (7/22). Descriptive statistics for all leukocyte and erythrocyte index values analyzed are shown in table 1. Lower hemoglobin (Hb) (subgroup median = 13 g/dL, range: 10.4 g/dL-14.8 g/dL, r = –0.494, p = 0.019; log-rank test: $\chi^2 = 0.9$, p = 0.3), hematocrit (HCT) (subgroup median = 39.3%, range: 30.0-44.5%, r = –0.445, p = 0.037; log-rank test: $\chi^2 = 0.6$, p = 0.4), and lymphocyte (subgroup median = 15.3%, range: 4.0%-21.5%, r = –0.421, p = 0.050; log-rank test: $\chi^2 = 3.7$, p = 0.05) counts, and higher baseline neutrophils (subgroup median = 75.6%, range: 69.7-86.9%, r = 0.404, p = 0.061; log-rank test: $\chi^2 = 5.7$, p = 0.02), were associated with longer survival time (Fig. 1), with a 10-month survival rate of 59% in individuals who met these parameters. After application of the aforementioned methods of correction for comparisons, none of the hematological indices described in table 1 reached statistical significance at the adjusted level (p < 0.05); however, the data corresponding to Hb, HCT, Lymphocytes, and Neutrophils presented the lowest adjusted p values through the Benjamini-Hochberg method (p = 0.198). The neutrophil-to-lymphocyte ratio, calculated as the absolute neutrophil count divided by the absolute lymphocyte count[8], did not correlate with survival span. Similarly, in this cohort, the monocyte-to-lymphocyte and the lymphocyte-to-platelet ratios did not correlate with survival span in CJD (data not shown).

Discussion

Here, we evaluated the association between the survival of Mexican people with CJD and the values obtained for the CBC. In the analyzed population, we observed a strong correlation between lower Hb and HCT values with longer survival, which concurs with observations in Chinese populations[1]. While our study is not designed to address causality, this may be due to the interaction of Hemin-PrPC, which promotes the increase of Hb synthesis in the erythropoietic pool[9]. Thus, the neurologic damage induced by PrPSc at the brain level can be interpreted as proportional to Hb and HCT counts[9]. On the other hand, we also observed a possible association between leukocyte counts and survival, probably attributed to PrPC located in peripheral blood CD34+ hematopoietic progenitor cells functioning as a cell receptor and precursor of PrPSc. Hematopoietic stem cells strongly express PrPC, with clear

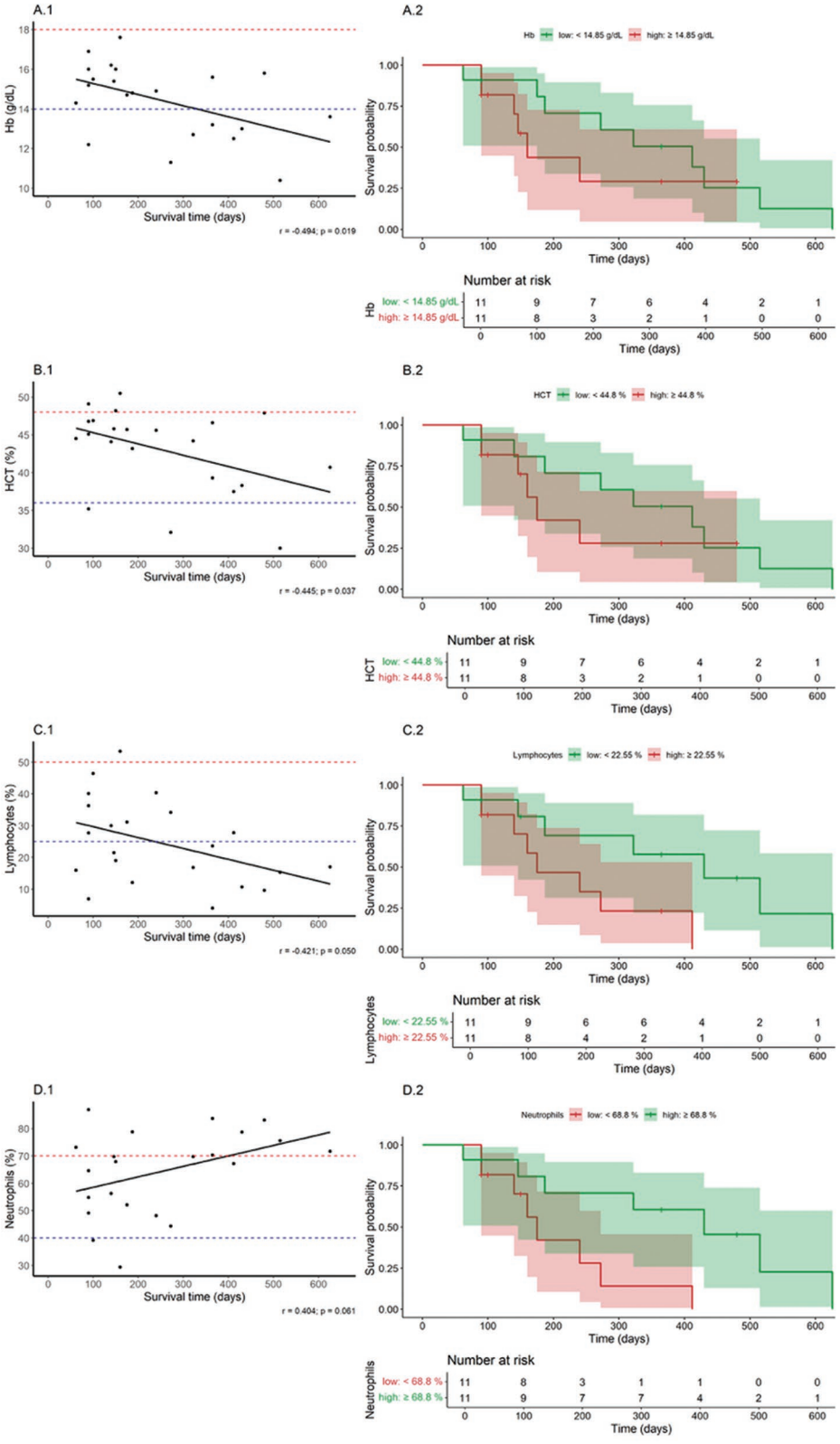

Figure 1. Association between survival time and leukocyte and erythrocyte abnormalities (X.1 – left figure: blue and red lines represent the lower and upper values, respectively, of the reference parameters used); and survival analyses with Cox proportional hazard models (X.2 – right figure) levels in people with Creutzfeldt-Jakob disease in Mexico. Hemoglobin (**A.1**, **A.2**), HCT (**B.1**, **B.2**), lymphocytes (**C.1**, **C.2**), and neutrophils (**D.1**, **D.2**).

lineage variability. During differentiation, the granulocytic lineage down-regulates PrPC, while PrPC expression is maintained in lymphoid lineages throughout the lifespan of the lymphocyte[10]. Hence, the granulocytic lineage expresses lower levels of PrPC in comparison to the lymphocytic lineage[11]. In our cohort, low levels of lymphocytes and high levels of neutrophils were associated with longer survival; as PrPC expression is needed to produce the misfolded (PrPSc) protein, we speculate that a shift to higher circulating numbers of low-PrPC-expressing granulocytes (and concomitant reduction in high-PrPC-expressing circulating monocytes) decreases the available pool of the PrPC needed as seed for PrPSc formation[12-14]. Our Hb and HCT observations are in agreement with previous reports[1]; however, we also observed that leukocyte markers predict survival span, something not previously observed. This may be due to genetic variability but also because our cohort is more female-tilted and younger than those in other studies[1].

This study has some limitations. First, we included a small number of people, which represents a possible limitation in terms of statistical power, by decreasing the ability to identify true associations. This limitation is reflected in the presence of trends that, although they do not reach statistical significance after the application of corrections for multiple comparisons, suggest possible relevant biological relationships; this is due in part to the rarity of CJD, but we also suspect that in Mexico, CJD is underdiagnosed due to a combination of a lack of familiarity with a rare disorder, with limited access to tertiary care in people with lower socioeconomic status, and those living far from tertiary care institutions. Furthermore, all cases are derived from only two institutions, potentially biasing the analysis due to geographic or financial constrictions. In addition, survival by subtype classification is not assessed for this cohort, since only one patient with a genetic diagnosis is reported. Our results are, in many ways, preliminary and will need to be replicated and validated in independent cohorts, and with a larger sample size. Nevertheless, these findings constitute a valuable starting point, as they represent the first Mexican pilot study focused on the analysis of hematological parameters and their possible correlation with the underlying pathophysiological mechanisms in prion diseases.

Conclusions

Our data indicate that certain parameters obtained in a routine baseline CBC, an inexpensive and ubiquitous blood test, can be useful in estimating the survival span of people with CJD.

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

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

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REVIEW ARTICLE

Health-related quality of life in Guillain-Barré syndrome patients: a literature review

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Abstract

Guillain-Barré syndrome (GBS) is the leading cause of flaccid paralysis and significantly affects functionality and health-related quality of life (HRQoL). While disability and muscle strength scales remain standard for assessing recovery, HRQoL offers a broader perspective by integrating physical, emotional, and social aspects often overlooked in clinical practice. The objective of this review is to synthesize current evidence on the tools used to assess HRQoL in patients with GBS and to analyze demographic, clinical, and paraclinical factors associated with outcomes. Longitudinal studies indicate that HRQoL is most impaired during hospitalization and early recovery, with gradual improvement over time. Worse HRQoL is associated with advanced age, prolonged mechanical ventilation, dysautonomia, sensory deficits, high disability scores, axonal variants, urinary dysfunction, depression, and post-traumatic stress disorder. Overall, the evidence highlights the need for a disease-specific HRQoL instrument and longitudinal studies to enable accurate evaluation and guide targeted interventions that improve long-term outcomes in GBS patients.

Keywords: *Guillain-Barré syndrome. Quality of life. Patient health questionnaire. Fatigue. Disability. Health-related quality of life.*

Calidad de vida en pacientes con Síndrome de Guillain-Barré: una revisión sistemática

Resumen

El síndrome de Guillain-Barré (SGB) es la principal causa de parálisis flácida y afecta significativamente la funcionalidad y la calidad de vida relacionada con la salud (CVRS). Si bien las escalas de discapacidad y fuerza muscular siguen siendo el estándar para evaluar la recuperación, la CVRS ofrece una perspectiva más amplia al integrar aspectos físicos, emocionales y sociales que a menudo se pasan por alto en la práctica clínica. El objetivo de esta revisión es sintetizar la evidencia actual sobre las herramientas utilizadas para evaluar la CVRS en pacientes con SGB y analizar los factores demográficos, clínicos y paraclínicos asociados con los resultados. Estudios longitudinales indican que la CVRS se ve más afectada durante la hospitalización y recuperación temprana, con una mejora gradual con el tiempo. Una peor CVRS se asocia con edad avanzada, ventilación mecánica prolongada, disautonomía, déficits sensoriales, puntuaciones altas de discapacidad, variantes axónicas, disfunción urinaria, depresión y trastorno de estrés postraumático. En general, la evidencia destaca la necesidad de un instrumento de CVRS específico de la enfermedad y de estudios longitudinales que permitan una evaluación precisa y orienten intervenciones específicas que mejoren los resultados a largo plazo en pacientes con SGB.

Palabras clave: *Síndrome de Guillain-Barré. Calidad de vida. Cuestionario de salud del paciente. Fatiga. Discapacidad. Calidad de vida relacionada con la salud.*

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Introduction

Guillain-Barré syndrome (GBS) is the leading cause of acute flaccid polyradiculoneuropathy worldwide, with a global incidence of 1-2 cases/100,000 people. It shows a predilection for the male sex, occurring more frequently in men than in women (0.86 vs. 0.57 cases/100,000 people per year, respectively)[1]. GBS is characterized by progressive, ascending, and symmetrical limb weakness, accompanied by reduced or absent deep tendon reflexes, mild sensory disturbances, and electrophysiological changes that allow classification and prognosis[2]. Despite timely diagnosis and treatment, 30-40% of patients experience an unfavorable functional prognosis in both the short and long term, leading to impaired quality of life (QoL) even when they achieve acceptable functionality[1,2].

GBS functionality can be assessed through the following three main measures: recovery of independent walking (using a disability scale), overall muscle strength (measured by the Medical Research Council [MRC] scale), and the modified Erasmus GBS outcome score, which predicts walking ability at 6 months. These parameters should be evaluated at hospital discharge and during follow-up visits[3]. The combination of the GBS disability scale (GDS) and the MRC scale with QoL assessments across various daily activities provides a more comprehensive view of functional recovery[4-6].

This review focuses on literature regarding key tools used to assess the QoL of GBS patients and analyzes demographic, clinical, and laboratory factors linked to both improved and reduced QoL.

Methodology

A structured review was conducted with the aim of identifying all studies that evaluated QoL in patients with GBS. The search used the keywords "Guillain-Barré syndrome" AND "quality of life" OR "health-related quality of life" in the PubMed, Scopus, and Embase databases, from January to May 03, 2025. Studies were included if they enrolled patients over 18 years of age with a diagnosis of GBS and employed at least one validated questionnaire to assess QoL. Case reports, case series with fewer than 10 patients, letters to the editor, and studies that did not report results on QoL assessment or associated factors of its deterioration were excluded. All articles published from 1950 to May 2025 were evaluated, where we found 153 total articles, 116 were eliminated, and the work was carried out with 37.

Health-related QoL (HRQoL) in GBS patients

HRQoL is a multifaceted concept that reflects how patients perceive their health, the impact of the disease, and the response to treatment. HRQoL assessment involves measuring both daily functioning and the degree of disability[7,8]. Although numerous studies have explored the effects of GBS on QoL, they differ significantly in methodology, employing various assessment tools, domains, cutoff points, timelines, measurement frequencies, and variables[9]. Since 1994, the World Health Organization has defined QoL as an individual's perception of their position in life within the context of their culture and value system in relation to their goals, expectations, standards, and concerns rather than the absence of disease[10].

The QoL domains of patients with GBS can be affected by demographic, clinical, and paraclinical factors, both at the time of hospitalization and during follow-up[9]. The tools used to assess QoL of GBS patients are either general questionnaires or those specific to neuromuscular diseases[9,11], such as the short form 36 (SF-36), the World Health Organization QoL Brief Version (WHOQoL-BREF), the SF-12, the sickness impact profile (SIP), the Nottingham health profile (NHP), the Centers for Disease Control and Prevention (CDC) healthy days and the individualized neuromuscular QoL questionnaire (INQoL), which is specific to peripheral neuropathy[9,12,13].

QOL of GBS patients from different perspectives (questionnaires)

During the follow-up of GBS patients, QoL has been studied at various intervals, ranging from 14 days to 10 years after acute episodes[9]. Studies have shown impairments across several areas, especially in physical function[4,5,14]. Over time, patients typically show favorable and progressive improvement, which is in line with the transitory course. The most significant recovery occurs within the first few months after an acute episode[15].

Longitudinal studies have reported that QoL measurements taken during the early stages of GBS, whether at symptom onset or during hospitalization, are directly influenced by clinical and paraclinical characteristics[16-18]. Long-term assessments have revealed

that GBS patients experience lower QoL than healthy individuals, mainly because of ongoing symptoms such as fatigue, pain, and lingering muscle weakness or sensory changes[19-22]. A patient's self-perceived ability to perform daily activities significantly impacts their QoL scores. This perception is closely tied to fatigue levels, which can be measured via the fatigue severity scale (FSS). Physical challenges and memory issues often persist for up to 2 years after the initial illness[23].

There is substantial evidence supporting the use of the SF-36 questionnaire to assess the QoL of patients with GBS. The SF-36 questionnaire consists of 36 items that evaluate the following eight domains: general health, physical role, physical function, bodily pain, vitality, mental health, emotional role, and social function. In addition, the SF-36 questionnaire provides two summary components: a physical component summary (PCS), which includes physical role, physical function, bodily pain, and general health; and a mental component summary (MCS), which includes social function, emotional role, mental health, and vitality[9,16]. Short-term evaluations (at 14 and 28 days and 1, 3, and 6 months) have revealed impairment across all domains, with progressive improvement over time[15,18], and long-term measurements (at 1 and 3 years) have indicated significant QoL impairment compared with healthy controls[24-27].

Long-term measurements have revealed persistent impairments in the QoL of patients with GBS**.** A case control study reported that 11 years after symptom onset, GBS patients exhibit deterioration across all SF-36 domains, with 80% lower scores compared to healthy controls[28]. Another study revealed that patients have worse QoL scores at 12 years after symptom onset than healthy controls[29].

The SIP is a tool frequently used for measuring QoL, and it has 136 items covering the following 12 physical and psychosocial domains: body care; mobility; ambulation; social interaction; emotional and wakeful behavior; communication; household management; sleep; rest; recreation and hobbies; eating; and work[9]. A study that assessed patients at 2, 6, 12, and 24 months of follow-up revealed significant impairment in eating during the first 2 months; in addition, sleep, recreation, and household management remained affected for up to 12 months, and physical function was still compromised at 24 months, with patients reporting slowed gait[30,31]. Another study conducted 10 years post-onset reported a significant decline in QoL compared with that of healthy controls, particularly in the physical domain[31].

The NHP questionnaire, which includes 38 items across six dimensions, such as physical mobility, pain, sleep, emotional reactions, social isolation, and energy levels, has been used to assess the QoL of GBS patients. A 6-month follow-up study revealed that GBS patients had significantly lower QoL than healthy controls[8].

The WHOQOL-BREF questionnaire has 26 items that assess four domains, namely, physical health, psychological health, social relationships, and the environment. The WHOQOL-BREF questionnaire has been used to assess GBS patients for 14 days, 28 days, 2 months, and 3 months after symptom onset, revealing progressive improvement across all the domains during follow-up. In addition, physical health and personal relationships were the most affected domains[32,33].

Evidence for the use of the INQoL to assess QoL of patients with GBS is limited. This 45-item questionnaire is divided into 10 sections as follows: four address the impact of motor neuropathy symptoms (weakness, myotonia, pain, and fatigue); five evaluate the impact of the disease on daily life (activities, independence, relationships, emotions, and body image); and one analyzes treatment, including its effects and expectations[34].

A study validated the usefulness of the INQoL in chronic neuromuscular diseases, including monoclonal gammopathy-associated polyneuropathy, multifocal motor neuropathy, and chronic inflammatory demyelinating polyneuropathy[35]. Another study used the INQoL during patient follow-ups at 14 days, 28 days, 3 months, and 6 months, revealing statistically significant differences over time; however, there were no significant changes in subscores or total scores between 14 and 28 days or between 3 and 6 months in the pain, social relationships, and emotions sections[12].

Using the INQoL instead of general or non-specific QoL instruments can provide more accurate assessments by targeting domains particularly affected by these diseases, such as fatigue and weakness, which are related to their pathophysiological characteristics and functional impact[36]. However, in the context of GBS, the acute or subacute nature of the INQoL presents a key limitation. Because the INQoL measure was designed for chronic diseases, its use could lead to an inaccurate evaluation of the impact of GBS on QoL.

The CDC healthy days questionnaire includes four core items and ten supplementary items that assess three categories, namely, physical health, mental health, and limitations in daily activities[37]. QoL assessments of patients using this instrument over different periods within 30 days revealed poor physical health

(58.8%, 29.4% and 11.7% of patients on Day 1, between Days 1-10 and after 10 days, respectively), poor mental health (67.6%, 11.7% and 20.5% of patients on Day 1, between Days 1-10 and after 10 days, respectively) and limitations in daily activities (67.6%, 11.7% and 20.5% of patients on Day 1, between Days 1-10 and after 10 days, respectively)[13].

Despite the use of different questionnaires, the previously mentioned studies agree that patients with GBS experience significant deterioration in their QoL at the time of hospital discharge. However, these patients show a gradual improvement in QoL scores and functional recovery over the following months. Nevertheless, some studies suggest that, even years later, patients fail to reach QoL levels comparable to those of healthy individuals.

Importantly, these questionnaires have limitations in accurately assessing patients with GBS, as these instruments are designed for chronic diseases and do not adequately address specific functional losses that characterize GBS. It is also important to consider the potential influence of modifiable and non-modifiable factors.

Factors related to impaired QOL

Studies have identified various factors associated with impaired QoL, each influencing the domains, components, and dimensions assessed by different questionnaires. Understanding these factors and their relationships with the aspects studied is essential for pinpointing specific areas that contribute the most to a decline in the QoL of these patients.

Demographic factors

Demographic variables influence HRQoL outcomes in GBS. Female patients consistently report lower scores, particularly in domains such as pain, social isolation, and physical mobility[8]. Low educational attainment and unemployment are also associated with greater impairment in psychosocial dimensions, including emotional reactions, sleep, and social participation. Age emerges as a predictor of long-term deterioration in the physical component of HRQoL, with older patients showing slower or incomplete recovery[23].

Clinical factors

Evaluations with the SF-36 at different follow-up points (14 days to 6 months) consistently showed that disability, measured by the GDS, strongly correlated with HRQoL, particularly in the physical domains[17]. Early impairment in SF-36 scores predicted poorer outcomes at 6 months. Similarly, studies using the NHP confirmed that physical mobility, energy, sleep, social isolation, and emotional reactions were more affected in GBS patients than in controls, with greater deterioration among those with depressive symptoms or functional dependency[8].

The INQoL also demonstrated close associations between disability and multiple domains of QoL, including weakness, fatigue, independence, and social roles. Interestingly, treatment modality influenced outcomes, such as patients receiving intravenous immunoglobulin reported worse QoL at 6 months than those treated with plasmapheresis[12].

Other clinical features, such as urinary dysfunction, pain, and fatigue, further compromised HRQoL. Up to 60% of patients experienced bladder symptoms, which many reported as interfering with daily life[38]. Pain, assessed with the McGill Pain Questionnaire, affected all subscales and was significantly correlated with both physical and mental components of HRQoL. Persistent neuropathic pain after rehabilitation was linked to worse vitality, emotional role, and social participation[19,39].

At 1 year of follow-up, SF-36 assessments revealed that age, early disability scores (GDS, MRC), and delays in hospitalization were consistent predictors of poorer HRQoL. Clinical complications such as antecedent infections, dysautonomia, cranial nerve involvement, neck muscle weakness, and the need for mechanical ventilation were also linked to worse outcomes, with treatment modality (plasmapheresis vs. immunoglobulin) showing an additional impact[19]. These findings reinforce that both baseline severity and acute complications determine long-term QoL.

In patients who required prolonged mechanical ventilation, follow-up with the SF-36 and NHP demonstrated persistent moderate disability. Notably, nearly one quarter developed post-traumatic stress disorder, which was associated with marked reductions in vitality, general health, mental health, and social function[29].

Long-term evaluations confirm that disability at onset strongly predicts persistent impairment in HRQoL. In studies with 6-10 years of follow-up, patients with higher GDS scores consistently showed greater deterioration in physical and psychosocial domains, and many remained functionally limited compared with healthy controls[22-24,40]. Age was also identified as a predictor of worse physical function in extended follow-up[40,41].

Table 1. Factors associated with poor quality of life during follow-up, organized by statistical level

Variables	Follow-up duration			
	6 months	1 year	2-3 years	> 5 years
Univariate analysis	Female, basic education, unemployment, depressive symptoms, high FIM score, immunoglobulin treatment, urinary symptoms[9]	Pain, diarrhea, neck muscle weakness, dysautonomia, involvement of cranial nerves, mechanical ventilation, axonal electrophysiological variants[18]	Mechanical ventilation for ≥ 2 months[28]	
Bivariate analysis	High GDS score[13]	Pain, advanced age, days between symptom onset and hospitalization, low MRC at symptom onset, low MRC at nadir, high GDS at symptom onset, high EGRIS at symptom onset, low MRC 1 year after symptom onset, high GDS 1 year after symptom onset, elevations of light neurofilament protein in CSF, high ODSS at symptom onset[18]		High GDS score at 6 months, NSS, high GDS score at discharge[22]
Multivariate analysis	High GDS score, low global score on SF-36 at 14 days[16]	Advanced age, diarrhea or respiratory infection, days between symptom onset and hospitalization, mechanical ventilation, dysautonomia, weakness of neck muscles, involvement of cranial nerves, low MRC score at symptom onset, low MRC score at nadir, high GDS score at symptom onset, plasmapheresis[18]		Advanced age, sensory deficit in upper and lower extremities, and high GDS score at 6 months[22,41]

CSF: cerebrospinal fluid; FIM: functional independence measure; GDS: GBS disability scale; MRC: medical research council; NSS: neuropathy symptom score; ODSS: overall disability sum score.

Paraclinical factors

Paraclinical findings further illustrate differences in prognosis. Patients with axonal variants consistently show poorer HRQoL across all SF-36 domains compared with those with demyelinating forms[19]. At 12 years after symptom onset, higher disability scores at baseline measured with both the GDS and the overall disability sum score were associated with poorer HRQoL, particularly in the physical and general health domains, and emerging biomarkers such as neurofilament light chain levels in cerebrospinal fluid are associated with greater impairment in physical and social function[30].

Factors that enhance QOL

Patients with the acute inflammatory demyelinating polyneuropathy variant and those treated with intravenous immunoglobulin generally report better HRQoL than those with axonal variants or treated with plasmapheresis[19].

Rehabilitation plays a central role in modifying these outcomes. Intensive programs are linked to reduced disability and improved functionality, although their benefit may be limited by the persistence of neuropathic pain[42,43]. Studies show that patients with ongoing pain after rehabilitation continue to report lower scores in vitality, emotional role, and social participation, highlighting the importance of addressing pain management alongside physical recovery[12,44,45]. Trials of rehabilitation programs, whether standard, intensive, or prolonged, consistently show functional gains and partial improvements in QoL, even if differences between high and low intensity regimens are not always significant[46,47].

An evaluation of low- and high-intensity rehabilitation in patients with GBS used the WHOQoL-BREF to measure QoL and the functional independence measure (FIM) to assess functionality at 12 months. The rehabilitation group was compared with a control group, as were the high-intensity group and the low-intensity group. No significant differences were found in the QoL scores between the groups. However, a significant improvement in FIM motor subscale scores was observed in the rehabilitation group compared with the control group. Comparison of the high-intensity group with the low-intensity group revealed significant differences in the overall FIM motor subscale scores[47].

When patients completed a 12-week program of three weekly cycling sessions, consisting of 5 min of warm-up and 30 min of exercise, they showed a 20% reduction in fatigue and significant improvements in

PCS and MCS scores of the SF-36 relative to healthy controls[48].

Patients who received physical therapy after hospitalization were evaluated with the SF-36 and FSS instruments at 7 years of follow-up. QoL and fatigue scores were compared between those who received physical therapy during or after hospitalization (90%) and those who did not (10%). Significant differences were observed, with greater deterioration in the physical function domain among patients without physical therapy, although no difference was found in FSS scores[49].

Rehabilitation over 12 weeks, delivered as outpatient physical therapy sessions of 60 min 2-3 times per week, was compared with a control group that received only a home exercise program for GBS patients. QoL was measured with WHOQoL-BREF at 6 and 12 months. Greater benefits were observed in the environmental domain at 6 months, whereas improvements in physical health and psychological domains were also evident at both 6 and 12 months[50]. A summary is presented of the factors related to QoL impairment across different follow-up periods, organized at the statistical level (Table 1). This allows the changes in each variable to be observed as other factors intervene, as well as the persistence of certain factors throughout the evaluation period.

Conclusion

Measuring QoL provides an integrated assessment of disease impact in both short- and long-term follow-up. It directly relates to disability, defined by independent walking ability, and to demographic (female), clinical (fatigue, pain, and dysautonomia), and paraclinical factors (neurofilament light chain levels in cerebrospinal fluid) at hospital admission, which clinicians often underestimate. These findings emphasize the need to evaluate HRQoL regardless of gait recovery or functional improvement, ensuring a more complete understanding of disease burden and supporting strategies to optimize patient outcomes.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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

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

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

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REVIEW ARTICLE

Optical imaging for human brain mapping

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Abstract

Optical imaging modalities for human brain mapping are noninvasive neuroimaging techniques that utilize light, typically in the near-infrared (NIR) wavelengths, to visualize and measure brain physiology and activity. These modalities provide critical insights into cerebral physiology by capturing hemodynamic and metabolic changes. They provide benefits such as real-time monitoring, portability, safety (no ionizing radiation), and cost-effectiveness. This comprehensive review outlines the current status of optical brain mapping technologies, highlighting key methods such as functional NIR spectroscopy and diffuse optical tomography while describing their effectiveness capabilities. It also traces the field's historical development from the past 10 years to current high-density optical imaging systems. Future directions are discussed, including emerging innovations to improve spatial resolution, depth penetration, and integration with other modalities, which promise to expand the utility of optical neuroimaging. These optical imaging techniques have become indispensable tools for neuroscience research and clinical brain mapping, and continued advances offer promising prospects for enhancing our understanding of the human brain.

Keywords: *Optical imaging. Brain mapping. Functional near-infrared spectroscopy. Neuroimaging.*

Imagenología óptica para cartografiar el cerebro humano

Resumen

Las modalidades de imagen óptica para cartografiar el cerebro humano son técnicas de neuroimagen no invasivas que utilizan la luz, normalmente en las longitudes de onda del infrarrojo cercano, para visualizar y medir la fisiología de la actividad cerebral. Estas modalidades proporcionan información esencial sobre la fisiología cerebral al captar los cambios hemodinámicos y metabólicos. Ofrecen ventajas como la monitorización en tiempo real, la portabilidad, la seguridad (sin radiación ionizante) y la rentabilidad. Esta revisión esboza el estado actual de las tecnologías de cartografía cerebral óptica, destacando métodos clave como la espectroscopia funcional en el infrarrojo cercano y la tomografía óptica difusa, al tiempo que describe sus capacidades. También traza el desarrollo histórico del campo desde hace diez años hasta los actuales sistemas de imagen óptica de alta densidad. Se analizan las direcciones futuras, incluidas las innovaciones emergentes para mejorar la resolución espacial, la penetración en profundidad y la integración con otras modalidades, que prometen ampliar la utilidad de la neuroimagen óptica. Estas técnicas de imagen óptica se han convertido en herramientas indispensables para la investigación neurocientífica y el mapeo cerebral clínico, y los continuos avances ofrecen perspectivas prometedoras para mejorar nuestra comprensión del cerebro humano.

Palabras clave: *Imagen óptica. Mapeo cerebral. Espectroscopía funcional en el infrarrojo cercano. Neuroimagen.*

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Introduction

Optical imaging modalities have significantly advanced over the past decade, becoming valuable tools for non-invasive human brain mapping. Techniques such as functional near-infrared spectroscopy (fNIRS), diffuse optical tomography (DOT), diffuse correlation spectroscopy (DCS), hyperspectral imaging (HSI), and photoacoustic imaging (PAI) measure neural activity and hemodynamics through light-tissue interactions. These methods are portable, safe, and cost-effective compared to magnetic resonance imaging (MRI) or positron emission tomography (PET), allowing bedside or naturalistic use, especially suitable for infants or active subjects[1]. fNIRS and DOT use near-infrared (NIR) light (650-900 nm) to detect oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) changes linked to neural activation[1]. DCS estimates real-time cerebral blood flow (CBF) by analyzing fluctuations of coherent NIR light[2]. HSI differentiates cortical tissues based on spectral reflectance, aiding tumor identification and assessing tissue oxygenation[3,4]. PAI combines optical contrast with ultrasonic detection, achieving deeper tissue penetration and high-resolution imaging despite skull-induced acoustic challenges[5]. From 2015 to 2025, these modalities have increasingly contributed to cognitive neuroscience, neurodevelopmental studies, and clinical neurology. A representative schematic of the modalities covered in this work is depicted in figure 1A. This review summarizes recent advancements, methodological trends, limitations, and future directions in optical brain mapping, following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines[6].

Methodology

Search strategy

We performed a systematic literature search to identify relevant studies from January 2015 up to March 1, 2025. The search encompassed multiple databases: PubMed/MEDLINE, Web of Science, Scopus, and IEEE Xplore, to capture both biomedical and engineering literature. We used Boolean search queries combining terms for optical imaging modalities and brain mapping. For example, the PubMed query is illustrated in figure 1B:

For reproducibility, the full Boolean search strings for each database are provided in table 1 of the Supplementary Material. We also hand-searched reference lists of relevant papers and prior reviews to ensure inclusion of any studies missed by the database search. All results were imported into a reference manager, and duplicates were removed[7]. This review was conducted following the PRISMA 2020 reporting guidelines[6], aiming for a transparent and reproducible selection process.

Prescreening and eligibility criteria

We included primary research articles meeting the following criteria: (1) published in English in peer-reviewed journals between 2015 and 2025; (2) involved *in vivo* human participants (either healthy individuals or patients) undergoing brain mapping with one or more of the optical modalities of interest (fNIRS, DOT, DCS, HSI, PAI); (3) reported functional brain data (e.g. neural activation, hemodynamic changes) or diagnostic imaging relevant to brain structure/function. We excluded animal studies, cadaver or phantom studies, technical papers without *in vivo* human data, editorials/commentaries, and conference abstracts.

The selection process proceeded in two stages. First, one reviewer screened titles and abstracts of all retrieved records for relevance to human optical brain imaging. Obviously, irrelevant records were excluded at this stage. Next, full-text of potentially eligible articles was obtained and assessed against the inclusion criteria. Studies that did not explicitly report results from human brains (e.g., purely simulation or algorithm development papers) were excluded. In total, the search identified n = 1,247 records after duplicate removal, of which n = 220 articles underwent full-text screening. Finally, n = 118 studies were deemed eligible and included in this review. A PRISMA 2020 flow diagram (Fig. 2) illustrates the study identification and selection process.

Risk of bias assessment

A formal risk of bias assessment was performed on the included studies to gauge the reliability of their findings. Given that many studies evaluated imaging modalities against clinical or neuroimaging benchmarks (diagnostic-type studies) or reported observational results, we employed the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool for quality assessment[8]. Each study was assessed in four domains: patient selection, index test, reference standard, and flow and timing. Signaling questions for each domain were answered based on information in the

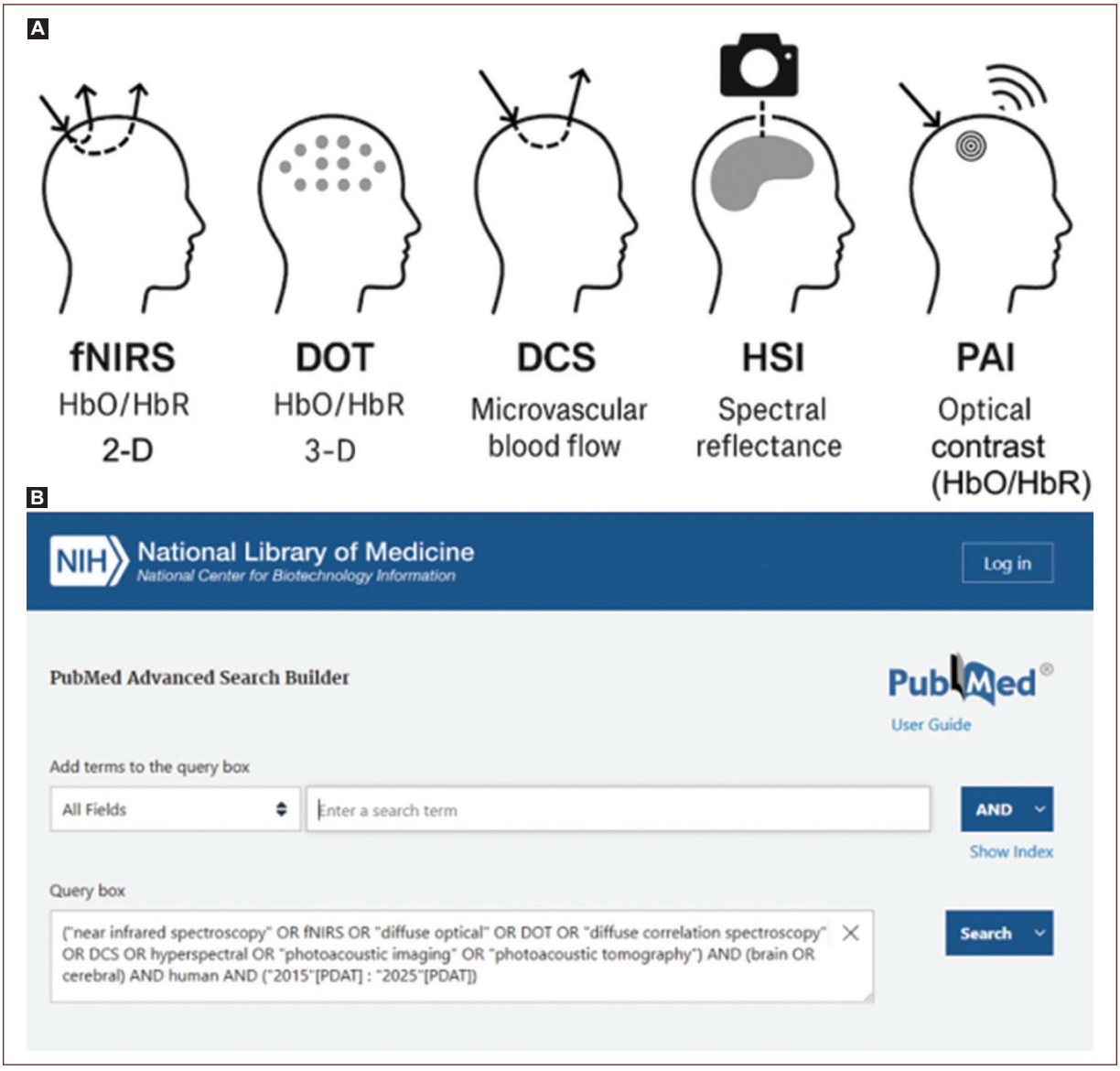

Figure 1. Overview of imaging techniques and literature search strategy. **A:** a representative schematic of the imaging modalities included in this review. **B:** example of a search query.

papers, and each domain was rated as "Low," "High," or "Unclear" risk of bias per guidelines[8]. A single reviewer (the first author) performed the risk of bias assessment for all studies. We acknowledge that having a single reviewer conduct the study screening and bias assessments is a methodological limitation; ideally, two or more independent reviewers would carry out these steps to strengthen rigor and reduce potential bias. Nevertheless, the reviewer adhered to the standardized QUADAS-2 protocol and consulted with co-authors regarding any uncertainties to mitigate subjectivity.

Results

A total of 118 studies met our inclusion criteria, encompassing applications of fNIRS, DOT, DCS, HSI, and PAI in human brain mapping from 2015 to 2025. We organized the findings by modality, highlighting key technical developments, typical applications, and overarching trends for each. These 118 primary studies form the basis of the results summarized by technique as shown in table 1.

Across optical brain-imaging methods, fNIRS and high-density DOT provide centimeter-deep cortical coverage with spatial resolutions of roughly 5-30 mm and

Table 1. Summary of 118 optical brain-imaging studies published 2015-2025, grouped by modality, typical human populations investigated, and representative key findings

Modality	Studies (n) 2015-2025	Typical human populations	Representative key findings
fNIRS	60	Healthy adults, infants, preschoolers, stroke, TBI, neuro-psychiatric cohorts	Portable systems enable naturalistic tasks, hyperscanning, and neuro-feedback; wearable caps combined with VR for social-development research
DOT	20	Adults, toddlers (1-7 year), epilepsy, peri-operative language mapping	High-density arrays provide fMRI-comparable cortical maps; feasible in awake children watching movies
DCS	15	Acute ischemic stroke, neuro-ICU, cardiac arrest survivors, healthy volunteers	Real-time bedside CBF monitoring; detects reperfusion after thrombolysis; reviews highlight no RCTs to date
HIS	13	Intra-operative brain-tumor patients (glioma, metastasis)	Spectral classifiers delineate tumor margins; first multi-site benchmark dataset released
PAI	10	Adults with hemicraniectomy, neonates (fontanelle), intra-operative vascular mapping	First transcranial functional PAI in a human; reviews outline roadmap and skull-mitigation strategies

fNIRS: functional near-infrared spectroscopy; DOT: diffuse optical tomography; DCS: diffuse correlation spectroscopy; HIS: hyperspectral imaging; PAI: photoacoustic imaging, CBF: cerebral blood flow, TBI: traumatic brain injury; ICU: intensive care unit; RCTs: randomized controlled trials.

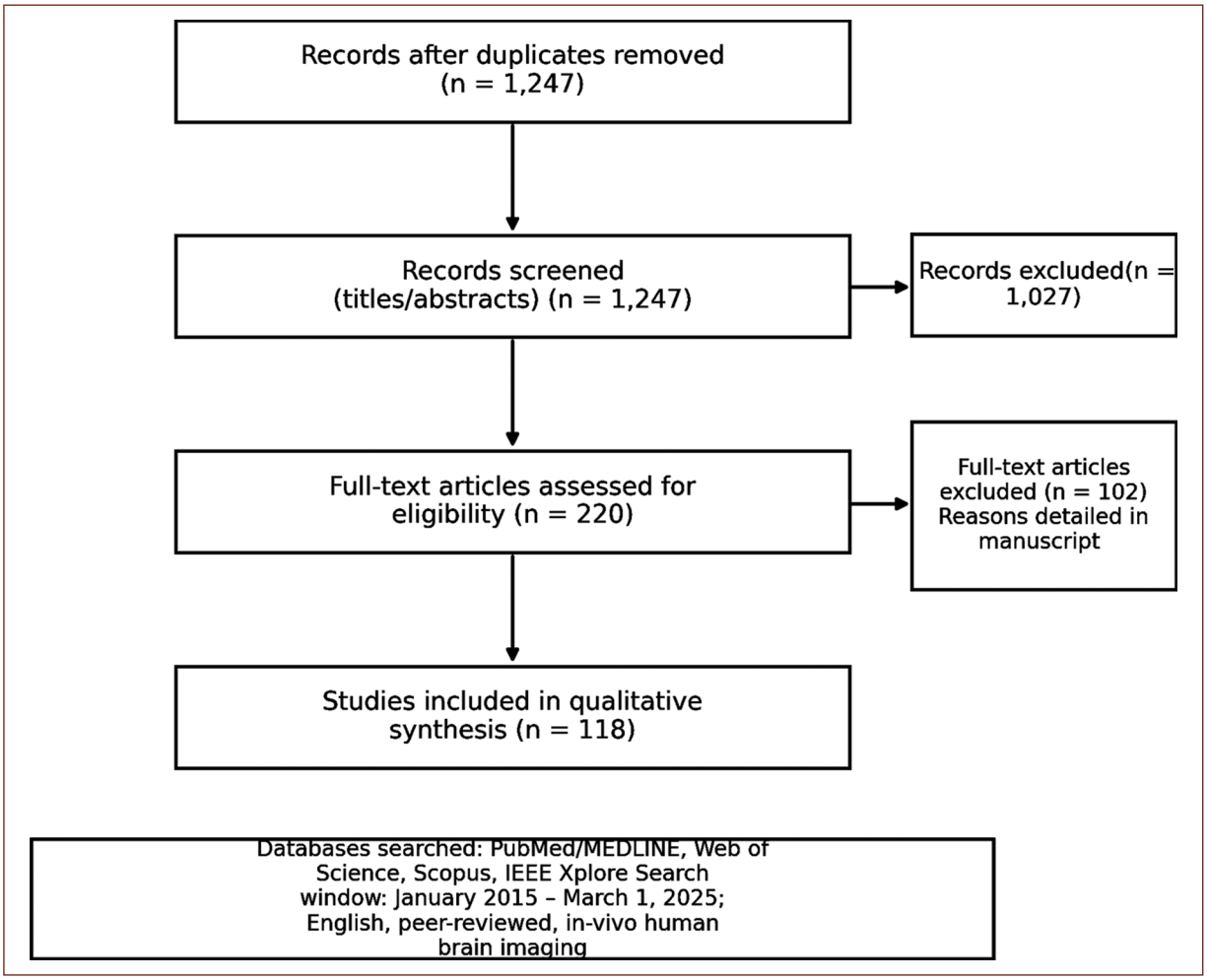

Figure 2. Preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram for study selection.

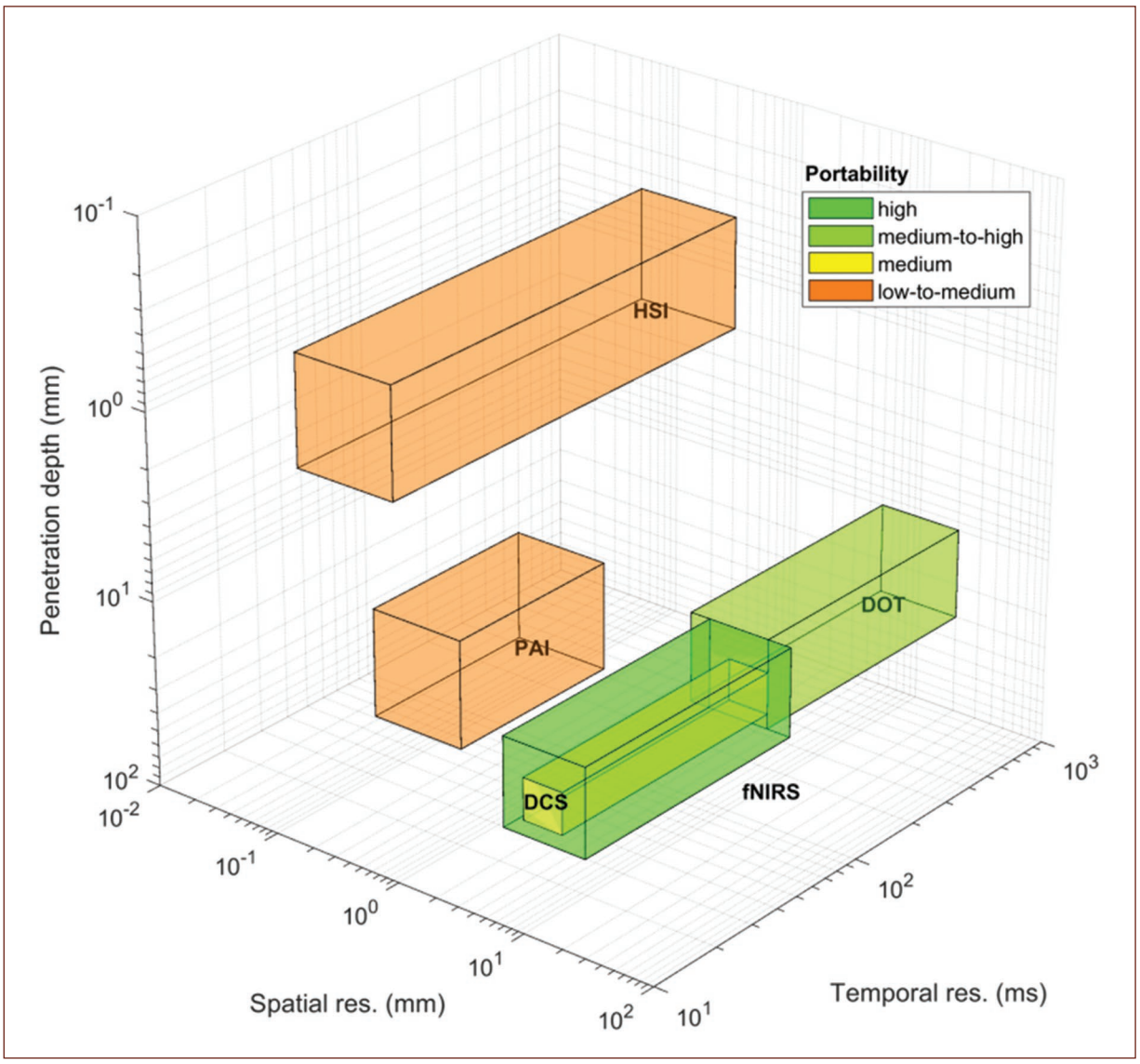

Figure 3. Comparison of the reviewed optical imaging modalities according to their temporal and spatial resolution, penetration depth, and portability.

the highest portability, while DCS offers similar depth but adds fast blood-flow metrics at moderate portability; HSI delivers sub-millimeter surface detail yet is limited to exposed cortex and remains less portable, and PAI uniquely penetrates up to several centimeters with sub-millimeter resolution but still faces skull-related constraints and lower portability. These results are summarized in figure 3.

fNIRS

fNIRS has become a widely used modality in human neuroscience over the past decade, reflecting its maturation into a robust functional imaging tool[1,9]. fNIRS uses sources and detectors placed on the scalp to measure changes in NIR light absorption associated with CBF and oxygenation changes in cortical regions[1]. From 2015 to 2025, there was an explosion of fNIRS research in diverse fields, including cognitive psychology, social neuroscience, developmental neuroscience, and clinical neurology[9-12]. This surge is evidenced by a large number of publications and review articles, which *"testifies to the maturity achieved by this non-invasive optical, vascular-based functional neuroimaging technique"*[1].

One important trend has been the deployment of fNIRS in naturalistic and mobile settings. Whereas early fNIRS studies (pre-2015) often occurred in laboratory environments with participants seated still, newer studies have leveraged advances in portable and wireless fNIRS devices. By around 2018, truly wearable fNIRS systems enabled recording brain activity in freely moving subjects during realistic tasks[13,14]. For example, researchers have used fNIRS to monitor prefrontal cortex activity while people navigate real-world environments or engage in social interactions, which is infeasible with functional magnetic resonance imaging (fMRI). Pioneering studies even conducted hyperscanning (simultaneous fNIRS on multiple people) to study interactive brain dynamics (e.g., teacher-student or parent-child interactions). These developments were facilitated by compact wireless emitters/detectors and Bluetooth data transmission, as well as improved signal processing to filter out motion and ambient light artifacts. Today, fNIRS is utilized on healthy subjects moving freely in different naturalistic settings, an achievement anticipated to grow with further instrument development[1].

In parallel with mobility, the spatial coverage and density of fNIRS arrays have increased. Traditional fNIRS used sparse optode arrangements, yielding only rough topographical maps. Recent high-density configurations place many optodes in a grid, with overlapping measurements at multiple source-detector distances. This approach, often termed high-density DOT, when paired with image reconstruction, dramatically improves image quality over sparse fNIRS[15]. For instance, Tripathy et al. built a high-performance high-density DOT system with an array of sources and detectors specifically designed to be child-friendly[15]. They demonstrated that such high-density fNIRS can produce image quality benchmarked against fMRI – mapping functional responses in 1-7 year-old children watching movies, a scenario where fMRI is challenging due to motion and compliance issues[15]. The ability to obtain spatially detailed maps of cortical activation (e.g., distinguishing functional responses in Broca's area vs. adjacent cortex during speech stimuli) has garnered significant interest in both cognitive and clinical research[16]. Indeed, high-density fNIRS/DOT approaches have achieved enough spatial resolution to resolve localized activation comparable to fMRI findings, while retaining fNIRS's logistical advantages (silent, portable, tolerant to motion)[15,16].

Applications of fNIRS in healthy populations have expanded to a wide array of cognitive functions – from language processing and auditory perception to decision-making, attention, and motor control. In clinical populations, fNIRS has been explored for bedside functional monitoring and neurorehabilitation progress. For example, multiple studies used fNIRS to assess motor cortex activation in stroke patients during rehabilitation tasks, finding that fNIRS activation magnitudes correlate with motor recovery stages (references in included studies). fNIRS has also been applied to monitor frontal lobe activity in disorders of consciousness, to map language or memory function in epilepsy patients, and even to assist brain-computer interface (BCI) development for patients with paralysis[17]. The data suggest that fNIRS signals (changes in HbO and HbR concentrations) can serve as biomarkers for brain function in situations where MRI is impractical or unsafe (e.g., early after stroke, in the intensive care unit [ICU], or in patients with motor deficits[12,18,19]). Furthermore, interactive neuroscience paradigms have emerged, such as neurofeedback training using real-time fNIRS signals and studies of how physical exercise modulates cortical activation[1].

Despite these advances, limitations of fNIRS remain. The technique is fundamentally limited to sensing cortical surface activity (typically ≤ 1.5 cm deep) because NIR light is strongly attenuated in tissue[9-11,20-22]. Signals are also contaminated by superficial blood flow in the scalp/skull (systemic physiology, skin blood vessels), which can confound true cerebral signals. A pressing need for standardized protocols to remove or account for these extracranial signal components has been identified[1,22]. Short-separation detectors (to measure and subtract scalp-only signals) and improved algorithms (e.g., regression of global trends, machine learning classifiers) are being incorporated to address this. In addition, because many fNIRS setups are custom, results can vary across labs. Efforts like near-infrared spectroscopy (NIRS)-brain imaging data structure (BIDS) (a BIDS extension) have begun standardizing data formats to improve reproducibility[23,24]. Before fNIRS can become a clinical neurodiagnostic tool, consensus on systemic interference correction, probe placements, and quantification methods is needed[1,9]. Nonetheless, the trend over 2015-2025 shows fNIRS evolving from a niche laboratory technique to a mainstream neuroimaging modality with growing real-world and clinical applications, thanks to its non-invasiveness and flexibility.

DOT

DOT extends fNIRS using high-density source-detector arrays and image-reconstruction algorithms to generate 3D maps of cortical HbO and HbR. Between 2015 and 2025, it matured into a tool that can approach fMRI-level localization when optode spacing is ≤ 1 cm and measurements overlap densely, driving widespread adoption in cognitive and clinical research[15,25]. Continuous-wave (CW) DOT dominates because the hardware is inexpensive and portable; a 2024 systematic review tallied 83 CW -DOT human studies, underscoring rapid growth[16]. High-density systems have mapped language in toddlers, neonatal strokes, and peri-operative cortex, tasks previously impractical for sparse optics or fMRI[26].

Algorithmic advances, regularized inverse models, MRI-based head priors, and multi-wavelength fitting now resolve activity in individual gyri and yield quantitative hemoglobin changes; DOT activation patterns routinely overlap with fMRI benchmarks[25,27]. Pilot clinical work shows promise for stroke, epilepsy, and intraoperative mapping, where neuronavigation-guided DOT offers an optical analog to fMRI[16].

Challenges remain

Image quality depends on head-model assumptions, depth sensitivity is predominantly cortical, and high-density caps can be cumbersome. Standardized protocols and deeper-penetrating time-domain or frequency-domain systems are needed to improve quantification and broaden adoption[16,28]. Nevertheless, DOT as of 2025 remains primarily a research tool. No DOT system is yet widely approved for clinical use, and further validation in multicenter studies is needed to establish its accuracy and reliability compared to gold standards.

DCS

DCS probes CBF by tracking speckle-intensity fluctuations produced by moving red blood cells under coherent NIR illumination, yielding a continuous index of microvascular perfusion that complements fNIRS/DOT oxygenation data[2,29].

Bedside utility is illustrated by Delgado-Mederos et al., who combined DCS and NIRS in five acute-stroke patients and detected reperfusion within 2.5 h of thrombolysis, ahead of repeat imaging[30]. Subsequent clinical reports extend monitoring to hypothermic circulatory arrest, traumatic brain injury, and post-cardiac-arrest care, where continuous CBF trends inform management when ultrasound or MRI are impractical[31,32].

Technical advances from 2015 to 2025 focus on signal-to-noise, depth, and coverage. Multi-speckle detection and parallelized cameras reduce variance and expand the field-of-view[2]. Longer wavelengths (1064 nm) improve penetration, while time-gated and time-domain DCS isolate late-arriving photons for deeper cortical sensitivity[33]. Hybrid systems integrate DCS with NIRS to estimate cerebral metabolic rate of oxygen or with DOT to create emerging 3D flow tomograms[29].

Limitations persist

Probes must remain immobile; absolute calibration requires external standards; adult measurements are confined to superficial cortex; and spatial localization is coarse unless high-density grids or MRI co-registration are used[2,29]. Nonetheless, progressive hardware miniaturization, depth-discrimination schemes, and early commercial devices position DCS as a valuable, real-time perfusion monitor poised for wider neurocritical and functional applications[33].

HSI

HSI records a complete reflectance spectrum for every pixel, yielding rich optical fingerprints that differentiate brain tissues without dyes. A systematic survey of clinical literature tallied > 25 operative HSI systems and 45 human studies, confirming rapid growth in neurosurgical use (though typically sample sizes were small)[34,35]. The foremost application is intraoperative tumor delineation: the HELICoiD consortium built an open VNIR database of 36 cubes from 22 glioma patients (> 300,000 labelled spectra) and showed that spatial-spectral classifiers could highlight tumor margins with ~ 80% accuracy in real time, guiding resection decisions[3]. A subsequent multicenter benchmark enlarged the dataset to 61 images from 34 patients and reported a median macro-F1 of 70% for tumor detection, establishing a common reference for algorithm development[36].

HSI also exploits hemoglobin absorbance to map cortical oxygenation and vascular anatomy during aneurysm repair, bypass grafting, or decompressive craniectomy, offering wide-field perfusion assessment that complements point probes[35]. Early reports indicate that task-evoked spectral changes can localize functional cortex in awake craniotomy, suggesting a

contact-free adjunct to electrical stimulation. Hardware advances have catalyzed translation: snapshot cameras using birefringent spectral demultiplexers now capture ≥ 64 spectral bands in a single exposure, delivering video-rate cubes compatible with the pulsating brain[37]. Compact modules mount on operative microscopes or exoscopes, allowing surgeons to toggle between white-light and hyperspectral views without workflow disruption[35]. Concurrently, deep-learning pipelines fed by public datasets generate color-coded overlays of tumor probability directly in the eyepiece, standardizing spectral interpretation and accelerating decision-making[3,4,36].

Despite these advances, HSI remains confined to the exposed cortex: reflected photons interrogate only the first few millimeters, leaving subsurface tumor or hemorrhage invisible. Image quality can be degraded by surface blood, irrigation fluid, or variable illumination, necessitating stringent calibration and spectral normalization[35]. Most clinical reports are single-center case series with modest cohorts; robust multicenter trials are still scarce, although the Leon benchmark represents a critical step toward standardization and external validation[36]. Active research goals include depth-resolved extensions (e.g., endoscopic or hybrid HSI-fluorescence systems) and harmonized acquisition protocols.

In sum, 2015-2025 saw HSI progress from proof-of-concept to a nascent operating-room adjunct that can delineate tumors, assess perfusion, and potentially map function in real time. While feasibility has been demonstrated in operative settings, HSI remains an experimental adjunct; no HSI system is yet cleared for routine neurosurgical use. Further, inter-patient variability in spectra means algorithms need robust calibration and possibly large training datasets to be reliable. As of 2025, HSI shows great promise for intraoperative guidance, but it will require larger trials (and possibly regulatory approval) to establish clinical utility.

PAI

PAI combines optical contrast with ultrasound detection to achieve deeper imaging than purely optical methods. In transcranial applications, PAI has been investigated in specialized scenarios – notably in patients with skull openings (e.g., hemicraniectomy or fontanelle in neonates) where acoustic coupling is feasible. About 10 studies from 2015 to 2025 applied PAI or photoacoustic tomography (PAT) to human brain imaging. One milestone was the first report of transcranial functional PAT in an adult human, achieved using a patient with a large skull defect to bypass skull attenuation[38]. Other studies imaged neonatal brains through the fontanelle, visualizing blood oxygenation changes during interventions. PAI has also been explored intraoperatively for vessel mapping or cerebral perfusion monitoring by applying an ultrasound detector over exposed brain tissue.

Technical innovations for PAI include using 1064 nm lasers (which penetrate bone somewhat better) and full-ring ultrasound detector arrays to capture signals from multiple angles[5]. Multiwavelength PAI has been employed in preclinical models to differentiate HbO versus HbR signals, yielding functional maps of oxygenation in the brain[5]. The primary challenge for human PAI is the skull: the bone greatly attenuates and distorts acoustic signals. Strategies such as skull thinning, cooling, or acoustic coupling media have been proposed to mitigate this, but remain experimental. Current PAI setups are also relatively bulky and require careful alignment of lasers and ultrasound sensors, limiting clinical practicality.

To date, PAI in humans is limited to feasibility demonstrations, and its clinical readiness is the most nascent among the modalities discussed. No large-scale human PAI studies exist yet, and safety considerations (ensuring laser exposure is within ANSI limits for skin/eye safety) must be managed as higher energies are considered for deeper imaging. Still, PAI's unique ability to provide high-resolution optical contrast at depth (by listening for photo-induced ultrasound) makes it a compelling future modality if technical barriers can be overcome. Reviews in the field have outlined a roadmap and remaining challenges for translating PAI into clinical neuroimaging[39,40].

Risk of bias and study quality

The overall quality of evidence across the included optical brain imaging studies is moderate, as assessed by our QUADAS-2-based analysis. Most studies were early-phase explorations, often lacking control groups or reference standards, which introduces various biases. Common issues included non-random participant selection (e.g., enrolling only young healthy adults for feasibility, or selecting patients with favorable conditions such as thin skulls or superficial tumors), which may overestimate the success of the modality in the general population. Blinding was seldom reported; for instance, investigators conducting fNIRS or DOT data analysis often knew the task conditions, and surgeons knew the ground truth of tumor locations when

evaluating HSI or PAI results, potentially biasing outcome assessment. Supplementary figure S1 provides an overview of the risk-of-bias ratings (low, high, unclear) across all included studies.

In studies where a reference like fMRI was used, some did not clearly state if the fMRI analysis was blinded to the optical results, raising the possibility of confirmation bias. Several patient studies (especially in stroke or ICU monitoring with NIRS/DCS) had no independent gold standard for the measured outcome, meaning they inferred clinical relevance indirectly (e.g., assuming that increased flow per DCS is good because the patient improved clinically, but without imaging confirmation). Flow and timing biases were present in longitudinal studies that had dropouts or where the optical measurement and reference test were not perfectly aligned in time. For example, in stroke monitoring, optical data were continuous, but the "ground truth" (such as an MRI scan) might have been done hours later, during which the patient's condition could have changed.

Another notable aspect is that many studies were small (median sample size 15 in our included set). This raises concerns about statistical power and selective reporting. Positive findings (e.g., successful mapping of a function or detection of a pathology) are likely over-represented in published studies, while negative or inconclusive studies may be underreported – a form of publication bias. This review cannot fully account for that, but it should be considered when interpreting the generally positive tone of results reported for each modality.

Encouragingly, some studies did incorporate measures to reduce bias: for instance, a few DOT versus fMRI comparison studies had independent analysts process each modality's data[15,25]; some HSI tumor studies used a third-party algorithm to classify spectra without knowing histology results[4,36], and then compared objectively. However, these were exceptions. The risk-of-bias assessment suggests that while the field demonstrates clear feasibility of each technology, the level of evidence is still preliminary, often in the form of case series or unblinded comparisons. There were no randomized controlled trials[16] and only a handful of multicenter studies[2,3,39]. Therefore, any quantitative performance metrics (tumor detection accuracy, stroke monitoring sensitivity, etc.,) should be considered provisional.

In summary, across modalities, there is a need for future studies with more rigorous designs: larger sample sizes, appropriate control conditions or reference standards, blinding of outcome assessments, and, if possible, multicenter collaboration to improve generalizability. The literature provides a strong proof-of-concept foundation, but the actual clinical utility and comparative performance of these optical techniques will require the next level of evidence.

Discussion and future directions

Over the last decade, optical imaging methods for human brain mapping have progressed from niche experimental techniques toward more mainstream neuroimaging and clinical research tools. Functional NIRS and DOT have seen the most widespread use, moving into real-world applications and complex populations (like infants and those who cannot undergo fMRI) while improving image quality. These modalities have clearly demonstrated feasibility for human brain mapping in research and even some translational clinical studies; however, they remain primarily research tools at present and have not yet achieved routine clinical adoption. DCS has added the capability to measure CBF, addressing a gap left by hemodynamics-only tools and opening new avenues in bedside monitoring. At the same time, DCS is still in an exploratory phase and requires further validation before it can be considered for standard clinical use. HSI and PAI, though still largely experimental in human brain applications, have demonstrated promising potential to provide rich spectral and high-resolution insights, respectively, although these results are still preliminary, especially in surgical or acute settings. At present, both HSI and PAI remain at a proof-of-concept stage in humans and are far from any routine clinical use.

The collective evidence from 2015 to 2025 indicates that these modalities can successfully detect functional activation and pathological changes in the human brain, but each comes with limitations that temper its current utility. Spatial resolution and depth remain key challenges: even with high-density DOT, optical methods cannot yet match MRI's sub-millimeter resolution or whole-brain coverage. Most fNIRS/DOT measurements are confined to cortical convexities, and deep structures (basal ganglia, hippocampus) remain noninvasively out of reach. PAI promises depth, but the skull's acoustic impedance is a formidable barrier. Efforts like using 1064 nm light and full-ring detectors[5] are partially mitigating this, and further innovations (e.g., skull cooling or coupling media to improve ultrasound transmission) are being considered. In parallel, the temporal resolution of optical techniques is high for

detecting hemodynamic oscillations (on the order of milliseconds for DCS speckle or instrument sampling, though physiological signals are slower). Still, they measure slower signals than neural electrophysiology. Integration with electroencephalography (EEG) or magnetoencephalography could provide a more complete picture of brain activity, combining fast neural and slower hemodynamic information.

A critical issue across modalities is signal quantification and specificity. fNIRS and DOT signals can be contaminated by scalp blood flow; standardizing short-separation regression and other preprocessing is a priority before clinical adoption[1,9]. DOT reconstructions need to become more quantitatively accurate (current images often require assuming bulk optical properties and use relative changes). DCS provides an index of flow, but calibrating it to absolute CBF is an area of ongoing research - one future direction is combining time-domain diffuse optics with DCS to independently measure optical path lengths and make DCS quantitative in absolute terms. For HSI, isolating the effect of one variable (say oxygenation) from others (such as blood volume or light scattering changes) is complex; advanced spectral unmixing algorithms and perhaps complementary measurements (like simultaneous NIRS for deeper layers) might help. PAI's specificity could be enhanced by multispectral PAT, taking images at multiple wavelengths to differentiate HbO versus HbR, lipid, and other tissue constituents. Indeed, multi-wavelength PAI has been used in preclinical studies to produce functional oxygenation maps of the brain and could be translated to humans to provide both structure and oxygenation in one modality[41].

From a technology standpoint, the next decade will likely see further miniaturization and integration. For fNIRS, one exciting avenue is the development of fully wearable, cap-based systems using flexible electronics and high-density grids that can record from most of the cortical surface. Some prototypes involve dozens of LED sources and silicon photodiode detectors embedded in a soft cap, powered by a battery pack or even operating wirelessly. These could turn fNIRS into a "wear it and forget it" technology for continuous brain monitoring in daily life or rehabilitation training. Similarly, integrating fNIRS and DCS in one device (as some research teams have done) provides a more complete hemodynamic picture (both oxygenation and flow). A logical next step would be commercial development of hybrid NIRS-DCS monitors for neonatal ICU or stroke units, which could noninvasively track cerebral oxygen delivery and utilization. The combination of flow and oxygenation can yield indices of metabolic rate (via Fick's principle), giving a window into brain metabolism at the bedside – a long-sought goal in neurocritical care.

Multimodal integration is another promising direction. We already see fNIRS being combined with fMRI (for cross-validation and to leverage fMRI's deep reach), with EEG (to support BCI designs where fNIRS provides complementary information to EEG signals), and even with transcranial electrical or magnetic stimulation (to measure brain hemodynamic response to neuromodulation). For example, concurrent EEG-fNIRS is used to study neurovascular coupling in epilepsy or to improve the accuracy of BCIs using two modalities. As we advance, one could envision trimodal systems (EEG + fNIRS + DCS) to monitor neural, hemodynamic, and perfusion changes simultaneously – this could be powerful in scenarios such as brain-computer interfaces for locked-in patients, where EEG might reveal intent and NIRS/DCS ensure adequate cerebral perfusion or track mental workload.

On the analytical front, the growing datasets from optical neuroimaging call for sophisticated analysis methods. Machine learning and deep learning approaches have started appearing for DOT image reconstruction and HSI spectral classification. For instance, deep neural networks can learn from examples of optical measurements paired with known brain activity (from fMRI or simulations) to directly reconstruct brain activation patterns, potentially outperforming traditional analytical models[42]. In HSI, deep learning is already used to improve the accuracy of tumor detection in the spectral images[43]. One challenge that ML can help with is denoising and artifact removal – for example, using convolutional neural networks to filter motion artifacts from fNIRS time series, or to correct for skull-induced distortions in photoacoustic data by learning the distortion patterns[5,42]. Caution is needed to ensure these models generalize and do not introduce bias, but early results are promising.

The field is poised for larger validation studies in terms of clinical translation and trials. For fNIRS/DOT, that might mean multi-site trials to test fNIRS as a tool for presurgical mapping of the language cortex (comparing it to the gold standard of direct cortical stimulation or fMRI). For DCS, a logical trial would be to validate DCS against established CBF measures such as PET or MRI-ASL (MRI-arterial spin labelling) in patients with cerebrovascular disease, to see how well DCS can track perfusion changes. If successful, DCS

could become an accepted monitor for conditions such as carotid stenosis or head-of-bed positioning effects in the ICU. HSI will likely see further clinical studies in neurosurgery: perhaps a Phase II trial of HSI-guided tumor resection, measuring if surgeons achieve more complete resection or better outcomes with HSI assistance (compared to standard white-light or 5-ALA (5-aminolevulinic acid) fluorescence guidance). PAI might initially find a niche in specific procedures – for example, monitoring cortical perfusion during cardiac surgery or neuroendovascular procedures, where a PAI probe could be placed on the head to watch for ischemia in real-time (something currently not done, but technically feasible with a craniotomy or thin bone window).

Regulatory and practical considerations will also shape future directions. Several fNIRS devices have already been approved for clinical use (e.g., for neonatal cerebral oximetry or functional brain imaging), but DOT systems and DCS are mostly confined to research. To translate, devices must be user-friendly and have cleared safety profiles. PAI systems will have to ensure laser exposure stays within ANSI (American National Standards Institute) limits for skin and eye safety; as energies increase for deeper imaging, ensuring no damage (especially to the eye from scattered light) is paramount. HSI devices should deal with issues such as sterilization (since they may be used in sterile fields) and real-time performance.

Finally, standardization and data sharing will significantly benefit the field. The past decade taught us that different groups sometimes reported divergent results for similar applications, likely due to differences in hardware or analytical choices. Initiatives such as open-source platforms for fNIRS (e.g. HOMER[44], AtlasViewer[45]) and shared datasets (like the DOI for the brain tumor HSI dataset[4]) should be expanded. A community consensus on reporting and comparing optical imaging findings (akin to the reporting standards in fMRI or EEG research) would help pool data and conduct meta-analyses. Applying the PRISMA framework in this review highlighted the need for more systematic reporting in optical neuroimaging studies themselves, such as more precise descriptions of participant selection and blinding.

Despite our focus on technological advances, it is important to acknowledge the limitations of our own review methodology. In particular, the study screening and quality appraisal for this review were conducted by a single reviewer. While this ensured consistency in applying inclusion criteria and bias assessments, it may also introduce subjective bias. Ideally, future systematic reviews in this area will involve multiple independent reviewers at each stage to enhance the reliability and reproducibility of the conclusions.

Conclusion

Optical imaging techniques have emerged as powerful tools for non-invasive human brain mapping, bridging gaps in traditional imaging modalities. Their versatility in clinical and naturalistic environments offers significant potential for advancing neuroscience and patient care. Future research should focus on standardization, quantification, multimodal integration, and rigorous validation through larger, multicenter studies. Enhancing depth penetration, spatial resolution, and real-time capability will further accelerate their translation from research to clinical applications, ultimately transforming how we understand and monitor the human brain.

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The author declares that this work was carried out with their own resources.

Conflicts of interest

The author declares that he/she has no conflicts of interest.

Ethical considerations

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

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

Declaration on the use of artificial intelligence (AI). The authors declare that an artificial intelligence tool was used to support the preparation of the manuscript.

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Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.25000039. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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REVIEW ARTICLE

Catatonia in clinical practice: from pathophysiology to treatment strategies

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Abstract

Catatonia is a complex neuropsychiatric syndrome involving motor, emotional, and behavioral symptoms. Once linked mainly to schizophrenia, it is now seen across various psychiatric, neurological, and medical conditions. Despite its prevalence, it remains underdiagnosed and undertreated, leading to serious health consequences. This review highlights the need for early recognition and intervention, discussing key diagnostic tools and treatments such as benzodiazepines and electroconvulsive therapy. It advocates for recognizing catatonia as a distinct clinical entity to improve clinical approach.

Keywords: *Catatonia. Benzodiazepines. Electroconvulsive therapy (ECT). Psychomotor syndrome. Diagnosis.*

Catatonía en la práctica clínica: de la fisiopatología a las estrategias de tratamiento

Resumen

La catatonia es un síndrome neuropsiquiátrico complejo con síntomas motores, afectivos y conductuales. Aunque antes se asociaba principalmente con la esquizofrenia, hoy se reconoce en múltiples trastornos psiquiátricos, neurológicos y médicos. A pesar de su frecuencia, sigue siendo poco diagnosticada y tratada, lo que conlleva graves consecuencias. Esta revisión destaca la importancia del diagnóstico y tratamiento temprano, abordando herramientas terapéuticas clave. Es importante reconocer la catatonia como una entidad clínica independiente para mejorar el abordaje clínico.

Palabras clave: *Catatonia. Benzodiacepinas. Terapia electroconvulsiva (TEC). Síndrome psicomotor. Diagnóstico.*

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Introduction

Catatonia a complex neuropsychiatric syndrome characterized by alterations in the motor, affective, and cognitive-behavioral areas. This syndrome is widely known in the psychiatric field, however, in the last years its conceptualization, diagnosis and treatment have been updated. Although often linked to schizophrenia, recent studies show that catatonia can also occur in various psychiatric and medical conditions, including mood disorders, neurological and autoimmune diseases, infections, and drug-related causes. This new conceptualization has led to updated diagnostic and therapeutic approaches, recognizing catatonia as a complex, multidisciplinary syndrome. However, detection remains clinically challenging, especially in non-psychiatric settings where symptoms may be mistaken for other conditions. This paradigm shift has important clinical implications, as misdiagnosis or delayed recognition can result in inadequate treatment, increasing morbidity and mortality.

The term *catatonia* was introduced in 1874 by German psychiatrist Karl Ludwig Kahlbaum (1828-1899), derived from the Greek *kata* ("down") and *tonos* ("tension"). He described 21 patients with unusual signs such as abnormal posturing, mutism, negativism, and catalepsy. Kahlbaum emphasized the affective component, noting that intense emotions often preceded catatonic episodes[1]. Emil Kraepelin (1856-1926) and Eugen Bleuler (1857-1939) advocated for including catatonia within dementia praecox (later termed schizophrenia) in psychiatric classifications. Kraepelin, particularly interested in its classification, defined catatonia as a subtype of dementia praecox in the sixth edition of his *Treatise on Psychiatry*. His work shaped the understanding of catatonia in the 19th and 20th centuries.

Following their contributions, catatonia was classified as a schizophrenia subtype marked by "prominent motor features" in systems such as the ICD and DSM[2]. In the past 20-30 years, interest in its features and underlying mechanisms has resurged[3]. The complexity of this syndrome, with its diverse forms of clinical presentation, makes it more likely to be identified not only in psychiatric units but also in general hospital settings, where it is more likely to be confused with other medical or neurological conditions. This underscores the importance of a comprehensive diagnostic and therapeutic approach.

Kahlbaum's original concept of catatonia as a complex syndrome involving affective, motor, and cognitive-behavioral dimensions, has been simplified by many clinicians, who focus mainly on motor/affective symptoms. Most clinical rating scales emphasize motor signs while neglecting affective and cognitive-behavioral aspects. Tools like the Bush-Francis Catatonia Rating Scale (BFCRS) prioritize features such as waxy flexibility and posture, leading to underrecognition of other critical symptoms. This narrow focus hinders early detection and treatment.

This conceptualization, focusing on motor or affective aspects of catatonia, is the one found in most of the current literature, which makes it difficult to provide adequate clinical care. The emphasis on motor signs tends to neglect affective and cognitive-behavioral symptoms, resulting in failure to detect catatonia, especially when motor features are not prominent. Consequently, this misperception can delay treatment initiation and may have negative consequences for patients.

Catatonia in the pediatric population is linked to significant morbidity and mortality. It is a distinct comorbidity seen in patients with genetic conditions, autism spectrum disorder (ASD), and other neurodevelopmental disorders. Fortunately, many cases respond well to timely treatment and interventions. However, diagnosing catatonia in this population presents challenges. Symptoms such as urinary incontinence, acrocyanosis, and schizophasia are frequently observed, but their presence can delay an accurate diagnosis. In addition, externalizing symptoms such as aggression and self-harm are more common in neurodiverse individuals with catatonia, further complicating clinical evaluation[4].

This review provides a comprehensive analysis of catatonia, reviewing its historical evolution, clinical presentation describing some particularities, pathophysiology, and current treatment strategies. By addressing current gaps in knowledge and emphasizing its broader clinical context, this article seeks to raise awareness and promote a reconceptualized approach to the recognition and treatment of catatonia in specialist and non-specialist physicians in the area.

Clinical manifestations

Since the presentation of catatonia may vary and present with different combinations of signs and symptoms, categorization must be individualized. Primarily, the evaluation focuses on a detailed observation of motor behaviors and the interaction of the patient with the evaluator and the environment. Within the examination, the evaluator must participate actively assessing the mobility, muscle tone, response to stimuli, and the ability to maintain or change postures. Furthermore, it is important to pay attention to the presence of automatic

behaviors (echolalia and echopraxia) or resistance to movement.

Signs of catatonia can be classified into three categories based on psychomotor behavior: increased, abnormal, and decreased, assessed by observation, interview, and physical examination (Table 1)[5]. Psychomotor behavior is considered abnormal when there is excessive reduction (akinesia), excessive increase (hyperkinesia), or when the motor act is presented abnormally (parakinesia)[6].

Many catatonic signs are triggered in response to the examiner and may depend on physical presence of the examiner. For example, the patient's mutism or hypokinesia may become more prominent in the presence of the evaluator but are typically transient, diminishing when the examiner leaves. An important feature of catatonia is the presence of autonomic abnormalities such as tachycardia, hypertension or fever but these are not present in all patients and particular attention should be paid to them due to their prognostic factor.

Pediatric considerations

With the pediatric population, it's important to keep in mind neurodevelopmental disorders, especially ASD. In these cases, the symptoms may overlap with catatonic syndrome, making clinical differentiation difficult. Careful assessment is required to determine whether episodes of aggression or regression represent a deviation from the patient's usual presentation or are simply part of their baseline symptomatology. Furthermore, autistic children with catatonia often exhibit increased impulsivity and aggression, adding another layer of complexity to diagnosis[7].

Clinically, catatonia in ASD manifests as a marked behavioral change, which helps distinguish it from baseline symptoms. However, overlapping features such as mutism, negativism, abnormal speech, rigid postures, and stereotypes can make differentiation challenging. A key diagnostic clue is that, in catatonia, these symptoms tend to appear suddenly or show significant deterioration compared to the patient's previous state. We summarize key points to take in mind for clinical evaluation in pediatric patients (Table 2)[4,8].

Treatment resistance is common in ASD-associated catatonia. Lorazepam response is often suboptimal. If antipsychotics are used, efficacy varies, and adverse effects must be carefully monitored[9].

This diagnostic approach not only helps to identify the clinical signs of catatonia but also distinguishes it from other neurological or psychiatric disorders with similar symptoms. Below are the main tests included in the directed examination for catatonia, which provide valuable information for the diagnosis and management of patient[9].

Catatonia can be classified into three different forms: akinetic catatonia, excitatory catatonia, and malignant catatonia, which depend on the intensity of the clinical manifestations and autonomic dysfunction. The most common form is akinetic catatonia, where patients show reduced motor activity, often staring and appearing unresponsive. Despite diminished reactions to verbal or painful stimuli, they remain conscious and aware. Contrary to common belief, many patients later recall these episodes, often describing them as distressing.

The second type is excitatory catatonia, which is characterized by an increase in the intensity of some signs, commonly observed when the patient presents apparently impulsive and aimless movements. Patients may show agitation, aggression, or even delirium. Excessive and intense motor activity can represent a danger to the patient as well as to others.

The third form characterized by being the most severe, malignant catatonia, is mainly characterized by autonomic instability, is often seen in the context of neuroleptic malignant syndrome (NMS) and may indicate an underlying medical condition that has a high mortality rate. Given its rapid progression, often in a matter of days, early recognition and immediate intervention are crucial to address the cause that generates it[10].

Another subtype described in the literature is periodic catatonia, marked by episodic fluctuations of motor symptoms such as rigidity, abnormal posture, and mutism lasting 4-10 days, followed by full remission. Its diagnosis is challenging due to the fluctuated nature. Dysfunction in the gamma-aminobutyric acid (GABA) system believed to underlie the condition, supported by positive responses to benzodiazepines. In some cases, atypical antipsychotics have also shown effectiveness[10].

A study in Mexico examined the coexistence of catatonia and delirium, conditions considered mutually exclusive in the DSM-5. Among 264 patients with delirium, 61 (23%) also met criteria for catatonia. Findings showed distinct associations: non-catatonic delirium was linked to brain tumors, subarachnoid hemorrhage, acute hydrocephalus, and ischemic stroke, while catatonic delirium was strongly associated with viral and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, epilepsy, and cerebral tuberculosis. An operational definition of catatonic delirium was proposed, requiring at least four specific signs on the BFCRS.

Table 1. This table outlines the 23 items of the Bush-Francis catatonia rating scale, along with the 12 DSM-5-TR items, marked with ✔. Additionally, it classifies the intensity of psychomotor activity and describes how each item can be assessed

Evaluation	Psychomotor activity	Concept	Definition	DSM-5 TR
Observation	Increased	Agitation, excitement	Extreme hyperactivity with unintentional movements and extreme, uncontrollable emotional reactions.	✔
		Impulsivity	The patient suddenly engages in inappropriate behaviors without provocation; afterward, they cannot provide an explanation or only offer a superficial one.	X
		Combativeness	Aggression toward others, with or without the potential to cause injury.	X
	Abnormal	Grimacing	Strange and inappropriate facial expressions, not in line with the context.	✔
		Mannerism	Exaggerated, rigid, or caricatured motor behavior that mimics normal actions in a strange or inappropriate manner.	✔
		Posturing	Spontaneous and active maintenance of a posture against gravity.	✔
		Sterotype	Repetitive and abnormally frequent movements that are not goal-directed.	✔
		Perseveration	Repetition, complete or partial, of actions or verbal content that is not goal-directed.	X
	Decreased	Stupor	No or markedly reduced psychomotor activity; no activity in relation to the environment.	✔
		Ambitendency	Appearance of being caught in indecisive or hesitant movements.	X
		Staring	Fixed gaze, reduced blinking, and wide-open eyes, or increased blinking.	X
Interview	Abnormal	Echolalia	Imitating another person's speech.	✔
		Echopraxia	Imitating another person's movements.	✔
		Automatic obedience	Mechanical and reproducible compliance with the examiner's requests, even if they are dangerous.	X
		Verbigeration	Continuous and undirected repetition of words, phrases, or sentences.	X
	Decreased	Withdrawal	No eye contact, refusal to take food or drink when offered, or both; turning away from the examiner or social isolation.	X
		Negativism	Opposition or lack of response to instructions or external stimuli.	✔
		Mutism	No or very little verbal response (exclude if aphasia is known).	✔
Physical examination	Abnormal	Mitgehen	Exaggerated movements in response to light pressure.	X
		Gegenhalten	Resistance to positioning by the examiner that increases proportionally to the force applied.	X
		Grasp reflex	Strong pressure of any object near the hand or touch.	X
		Rigidity	Resistance due to increased muscle tone.	X
		Catalepsy	Passive induction of a posture maintained against gravity.	✔
		Waxy flexibility	Mild and uniform resistance to positioning by the examiner.	✔
Autonomic abnormality			Diaphoresis, palpitations, abnormal temperature, blood pressure, pulse, respiratory rate.	X

Table 2. This table provides a quick and practical evaluation of the 14 key signs of catatonia and pediatric clinic considerations, aligned with the Bush-Francis catatonia rating scale. Ideal for initial screening in clinical or emergency settings

Initiating conversation	The examiner attempts to engage the patient in dialogue to assess for mutism, echolalia (involuntary repetition of another person's spoken words) or verbigeration (repetitive, meaningless utterance of stereotyped words or phrases).	Mutism may be confused with extreme anxiety or selective mutism. Echolalia may be an early sign of catatonia or a feature of autism spectrum disorder.
Exaggerated head scratching	The examiner scratches their head in an exaggerated manner, observing if the patient exhibits echopraxia (involuntary imitation of another person's movements or gestures).	Echopraxia may present as automatic repetition of movements from others or from media characters. It can be mistaken for playful imitation.
Muscle tone and posture tests	The patient is asked to relax their arm while the examiner observes for waxy flexibility (tendency to maintain limbs in positions in which they are placed, as if molded like wax), catalepsy (a state of muscular rigidity and fixed posture, with diminished response to stimuli), or gegenhalten (resistance to passive movement that increases proportionally to the force applied). The examiner may also attempt to change the patient's posture to assess rigidity or resistance.	Catalepsy may appear as unusual rigidity in forced positions, which could be misinterpreted as disinterest or extreme fatigue.
Arm extension test	The patient is instructed to extend their arms and maintain the position. The examiner then attempts to lift the arms, observing for mitgehen (the patient's arms moving involuntarily with the examiner's motion).	Mitgehen may be subtle and confused with an exaggerated response to physical contact or lack of motor control.
Negativism test	The examiner gives a simple instruction (e.g., 'raise your arm') and observes whether the patient does the opposite or resists without clear reason, indicating negativism (resistance or opposition to instructions or external stimuli, either actively or passively).	Negativism may be misinterpreted as oppositional behavior or stubbornness, especially in the context of neurodevelopmental disorders.
Response to painful stimuli	A mild painful stimulus (e.g., nail pressure) is applied to assess response; absence of reaction may indicate stupor (a state of unresponsiveness with immobility and mutism) or rigidity (sustained muscle tension with resistance to passive movement).	Lack of response to painful stimuli should be differentiated from pain desensitization seen in certain neurodevelopmental disorders.
Review of clinical records	Clinical records are reviewed for autonomic signs (e.g., fever, blood pressure changes) and reduced intake (e.g., food or fluids), which may indicate a catatonic state.	Dehydration and rapid weight loss may be key early signs, as catatonia can interfere with eating and hydration.

These results support the concept of catatonic delirium and challenge the DSM-5 classification of catatonia as a psychotic disorder. Given its strong association with autoimmune encephalitis and potential adverse reactions to antipsychotics, further studies are needed to reconsider DSM-5 criteria for catatonia due to another medical condition[11].

Recognizing the various forms of catatonia is key to accurate diagnosis and management especially in malignant catatonia, where early signs like autonomic instability are critical to prognosis. Symptom fluctuation in periodic catatonia adds diagnostic complexity, requiring close attention to the clinical course, even during apparent remission. Physicians must be aware that catatonia can present subtly or be masked by other psychiatric or medical conditions. A high index of suspicion and familiarity with the catatonic spectrum enable timely diagnosis and treatment, reducing the risk of life-threatening complications.

Epidemiology

The lack of a standardized definition and the diverse, overlapping symptoms of catatonia with other disorders make it difficult to assess its true incidence. Still, it is estimated to affect 5-18% of psychiatric inpatients and 3.3% of patients in tertiary neurology or neuropsychiatry units, with prevalence varying by underlying or comorbid conditions[12].

About 20% of reported cases of catatonia are a consequence of various general medical conditions. Infectious and autoimmune conditions (AIC) account for about 29% of cases related to medical causes. Among these, meningitis, encephalitis, and systemic bacterial, viral, or fungal infections are among the major contributors. AIC such as anti-NMDAR encephalitis and systemic lupus erythematosus show a strong association with catatonia. Notably, anti-NMDAR encephalitis accounts for 72% of autoimmune catatonia cases[13].

Given these statistics and the context, it would be prudent to initially consider catatonia in high-risk populations and use standardized tools for screening, particularly in non-psychiatric settings where it may be missed.

In recent years, there has been an increase in the reported incidence, which could be attributed to a higher prevalence of the disease, the increase in substance use, and the use of new psychotropic drugs and largely to changes in diagnostic criteria. Diagnostic heterogeneity, comorbidity with other disorders, and lack of case reporting are the main challenges in epidemiological research on catatonia[14].

Catatonia is rarely identified in pediatric patients (< 18 years) in general hospitals, often overshadowed by other serious medical and psychiatric conditions. A 2019 study in the USA reviewed 900 pediatric hospitalizations with a discharge diagnosis of catatonia (291 primary and 609 secondary). The mean age was 15.6 ± 2.6 years, with 9.9% under 13 years. The most common psychiatric diagnoses were psychotic disorders (18.3%), major depressive disorder (7.7%), bipolar disorder (4.3%), and substance-related disorders (2.2%) which make us consider psychotic disorders as the first suspicion in this population, unlike the adult population where affective disorders are the main cause[15].

Around 10% of people with ASD develop catatonia. This condition affects males much more frequently, making up between 70% and 100% of cases. It usually begins in late adolescence, most commonly between the ages of 15 and 19[7].

Catatonia in ASD frequently coexists with intellectual disability, with reported rates varying from 5.7% to 81%. In addition, obsessive-compulsive symptoms may precede catatonia, often accompanied by decreased speech, agitation, and self-injurious behavior[7].

In the older population, the prevalence of catatonia varies based on the setting and diagnostic criteria used. In liaison psychiatry services using the BFCRS, the prevalence was 5.5% and 8.9%. A study in an acute inpatient general psychiatry ward reported a prevalence of 11.2% with the BFCRS and 6.1% with DSM-5 criteria. The prevalence was higher in acute psychogeriatric units in the UK (27%) and Spain (24.3%), with the BFCRS and DSM-5 showing 39.6% and 20.8%, respectively[16].

Despite the diagnostic challenges, it is crucial to emphasize the significant clinical context across all age groups and the impact on morbidity and mortality.

Pathophysiology

It's important to understand the term "psychomotor," defined as the interaction between psychological processes and motor functions. In catatonia, this link is evident when psychological states, such as intense anxiety, manifest as motor disturbances such as paralysis, mutism, stupor, or catalepsy. This highlights how affective or cognitive changes can rapidly induce behavioral and motor disturbances.

The psychomotor nature of catatonia parallels neurodegenerative disorders such as Parkinson's and Huntington's disease, where non-motor symptoms (mood or cognitive disturbances) often precede and influence motor manifestations. Although modern brain models distinguish motor, affective, and cognitive networks, the complexity of catatonia suggests that these domains are interconnected, with frequent overlap[16].

The overlap of motor, affective, and cognitive symptoms in catatonia underscores the need for a broader neuropsychiatric perspective. Rather than viewing it solely as a movement disorder, its psychomotor features suggest dysfunction in brain circuits integrating emotion, cognition, and movement. This approach could improve diagnosis and treatment, highlighting the value of early detection and multimodal interventions.

Some theories propose that catatonia is a primitive defense mechanism – akin to tonic immobility in animals – triggered inappropriately by modern stressors. Its association with anxiety, depression, and responsiveness to benzodiazepines supports this view. Catatonia may represent a universal reaction to extreme threat, offering insights into broader psychiatric conditions[17]. Upcoming sections will explore the biochemical and neural mechanisms underlying its complex pathogenesis and treatment.

GABAergic dysregulation in catatonia

The potential mechanism that generates catatonia has been documented to be a dysregulation in the GABAergic system, particularly through the GABA-A and GABA-B receptors. A decrease in GABA-mediated inhibition can generate neuronal hyperexcitability, which

manifests with psychomotor symptoms and affective alterations. This substrate is consistent with the therapeutic quality of positive allosteric modulators of the GABA-A receptor[18,19].

Neuroanatomical pathways

Three key motor pathways are generally described in the pathophysiology of catatonia. The first pathway connects the primary motor cortex (M1) to the putamen, medial and lateral pallidum, and thalamus, and back to M1. This circuit is responsible for regulating the inhibition and intensity of movements. The second pathway connects M1, thalamus, cerebellum, and pontine nucleus, controlling the dynamics and timing of movements. The third pathway involves M1, the supplementary motor area (SMA), the posterior parietal cortex, and the medial prefrontal cortex, responsible for the organization and speed of movements. Dysfunction in any of these circuits may underlie the motor abnormalities observed in catatonia[20].

Dysregulation of the interaction between the SMA and the basal ganglia has been described in both schizophrenia and catatonia. In schizophrenia, reduced SMA activity is associated with motor deficits, whereas in catatonia, SMA hyperactivity has been detected, probably as a compensatory response to basal ganglia dysfunction. This hypothesis is supported by the efficacy of drugs such as lorazepam, which modulate basal ganglia activity and influence SMA function, resulting in improvement of motor symptoms[21].

Furthermore, in catatonia, reduced GABA activity, particularly at GABA-A receptors in the right lateral orbitofrontal cortex and right posterior parietal cortex, is thought to play an important role. This alteration in inhibitory signaling may explain both the motor and emotional symptoms characteristic of the syndrome. It also provides a rationale for the marked efficacy of benzodiazepines, which enhance GABAergic signaling and remain the cornerstone of catatonia treatment[21].

Catatonia results from both neuroanatomical and molecular dysfunctions. Hyperactivity in the SMA may compensate for basal ganglia deficits, while reduced GABA-A receptor activity disrupts inhibitory signaling in cortical regions. This dual disruption explains catatonia's varied symptoms and the effectiveness of benzodiazepines, which enhance GABAergic transmission and stabilize cortico-subcortical circuits[16]. These insights offer a unified framework linking molecular and anatomical factors in catatonia's pathogenesis and treatment.

Diagnosis

Catatonia is primarily diagnosed using the DSM-5-TR and ICD-11, though their criteria differ slightly. Clinimetric tools like the BFCRS are commonly used due to their accessibility and ease of use. In addition, therapeutic tests such as the lorazepam challenge are employed, with further details provided in the treatment section.

The DSM-5-TR classifies catatonia into three types: associated with another mental disorder, due to a medical condition, and unspecified catatonia. Diagnosis requires at least 3 of 12 defined symptoms. Rather than a standalone disorder, catatonia is recognized as a syndrome linked to various psychiatric and medical conditions[22].

ICD-11 classifies catatonia as an independent syndrome that can co-occur with various conditions, including psychiatric, medical, or substance-related disorders. Diagnosis requires at least three symptoms from categories of decreased, increased or abnormal psychomotor activity. It includes four subtypes: associated with mental disorders, substance/medication-induced, secondary catatonic syndrome, and unspecified catatonia[23].

Both classifications emphasize identifying catatonic signs and their link to medical or psychiatric conditions. The key difference is that DSM-5-TR links catatonia to underlying disorders, while ICD-11 treats it as an independent syndrome, allowing diagnosis without a clear cause. This reflects differing approaches: DSM-5-TR prioritizes etiology, whereas ICD-11 focuses on clinical presentation. Both systems are complementary, and their use depends on clinical context and professional needs.

A key innovation in ICD-11 is the inclusion of autonomic abnormalities, enabling the specification of malignant catatonia. ICD-11 also recognizes catatonia's temporal variability, which may present acutely, chronically, or fluctuate within a single episode. Unlike earlier versions, it allows a catatonia diagnosis even in the presence of delirium, if symptoms are not fully explained by it or another condition. These updates aim to enhance diagnostic sensitivity and promote earlier recognition across diverse clinical settings[24].

A summary table will be added below comparing the diagnostic criteria for catatonia according to DSM-5-TR and ICD-11, highlighting the main differences and similarities between both systems (Table 3)[22,23].

A systematic review identified seven rating scales for assessing catatonia in clinical settings: the Modified Rogers Catatonia Scale, the Rogers Catatonia Scale, the Northoff Catatonia Rating Scale (NCRS), the Braunig Catatonia Rating Scale (BCRS), the Kanner Scale, and the BFCRS[25].

Table 3. Provides a clear and concise comparison of the diagnostic approaches to catatonia in the ICD-11 and DSM-5-TR, highlighting their similarities and differences

Aspect	ICD-11	DSM-5-TR
Classification	Independent syndrome or associated with other disorders	Specifier for other mental or medical conditions
Symptom criteria	3 or more symptoms for at least 24 h	3 or more symptoms, no minimum duration specified
Etiology	Allows catatonia without a specific cause	Always requires an underlying cause
Focus	More flexible and descriptive	More tied to specific disorders
Subtypes	Catatonia associated with mental disorders, drug-induced, secondary, and unspecified	Catatonia associated with mental disorders, due to another medical condition, and unspecified
Autonomic symptoms/ Clinical course	Includes autonomic dysfunction and allows diagnosis even with delirium if catatonia is distinct	Doesn't emphasize autonomic symptoms; catatonia is excluded if better explained by delirium

Among these, the BFCRS, NCRS, and BCRS demonstrated the highest reliability across diverse populations. Another study evaluated three diagnostic tools the Bush-Francis screening instrument (BFCSI), the BFCRS, and the DSM-5 highlighting the superior sensitivity of the BFCSI in detecting catatonia cases. Notably, the DSM-5 criteria failed to identify nearly 64% of cases, underscoring the need for more precise diagnostic approaches in clinical practice[26,27].

BFCRS is a widely used tool for identifying and assessing the severity of catatonia. Comprising 23 items 14 of which form the screening instrument (BFCSI), it is valued for its ease of use, strong interrater reliability, and clinical validity. Its strong sensitivity and specificity make it effective in minimizing false positives, making it essential in psychiatric and neurology settings for early detection[28].

BFCRS is administered through direct observation of behaviors during clinical assessment and neurological examination. While it is typically scored over a minimum period of 5 min, it also allows for the incorporation of data on autonomic disturbances and withdrawal documented in nursing records from the previous 24 h[25].

Complementary studies

At present, there are no imaging studies or biomarkers sensitive enough to diagnose catatonia. Small clinical studies have investigated associations with inflammatory and acute-phase markers in catatonia but their role remains inconsistent.

A large-scale retrospective study found that patients with catatonia had lower serum iron levels compared to other psychiatric inpatients (11.6 vs. 14.2 μmol/L) and significantly elevated creatine kinase levels (2545 vs. 459 IU/L), suggesting potential muscle damage, secondary to motor symptoms. Notably, no significant differences were observed in C-reactive protein (CRP) or white cell count, indicating that systemic inflammation may not be a primary feature of catatonia[14].

Studies have found moderately elevated CRP and D-dimer levels in catatonic patients, suggesting inflammation and a potential risk of venous thromboembolism. Increased creatine kinase may result from muscle rigidity or immobility, raising the need to distinguish catatonia from NMS. Low serum iron, linked to dopamine synthesis, is also associated with higher NMS risk. While these biomarkers lack diagnostic specificity, they may aid in understanding mechanisms or assessing risk when interpreted carefully[13,29].

Although not routinely used, electroencephalography (EEG) has been employed to assess catatonia. A meta-analysis of 355 studies (707 patients) evaluated its role in distinguishing medical from psychiatric causes. In larger studies ($n \geq 5$), EEG showed 82% sensitivity and 66% specificity for medical causes (AUC = 0.83); smaller studies ($n < 5$) showed 76% sensitivity and 67% specificity (AUC = 0.71). Findings such as limbic abnormalities, epileptiform discharges, and non-convulsive status epilepticus were highly specific for medical catatonia. Encephalopathic slowing, seen in 23% of psychiatric cases, had moderate specificity. While EEG alone is insufficient for diagnosis, it can aid in uncertain cases when combined with clinical and complementary evaluations, helping differentiate organic from psychiatric origins[30].

Medical and psychiatric workup for pediatric catatonia

A thorough clinical evaluation is essential and should include multiple diagnostic studies. Brain magnetic resonance imaging (MRI) with and without contrast, pelvic or scrotal ultrasound, EEG, lumbar puncture, and comprehensive serum laboratory tests should take in mind. Other

assess antinuclear antibodies, antithyroid peroxidase antibodies (anti-TPO), antithyroglobulin antibodies, complete blood count, complete metabolic panel, myelin oligodendrocyte glycoprotein antibodies, NMDAR antibodies, and erythrocyte sedimentation rate could be helpful.

Given the high prevalence of genetic comorbidities in pediatric catatonia, genetic consultation is recommended whenever available. Post-operative catatonia has been reported in some cases and should be considered as part of the differential diagnosis.

Drug withdrawal or exposure can also trigger catatonia. Cases have been reported in infants following vaccine administration. In children, implicated drugs include haloperidol, ondansetron, and cyclosporine. Meanwhile, in adolescents, catatonia has been associated with chlorpromazine, benztropine, and olanzapine[31].

Autoimmune encephalitis is a closely related comorbidity that should always be considered in the evaluation of catatonia. While some treatment approaches overlap, key distinguishing factors include the use of immunomodulators, seizure occurrence, and the presence of an extreme brush-delta pattern on EEG[32].

Treatment

Catatonia treatment focuses on three main areas: managing the syndrome itself primarily with benzodiazepines or electroconvulsive therapy (ECT) addressing underlying medical or psychiatric conditions and preventing complications from immobility or psychomotor agitation. Lorazepam is a key treatment regardless of cause. Early intervention is crucial, as prolonged illness may reduce responsiveness, making prompt treatment essential[33,34].

Benzodiazepines

As previously noted, catatonia involves GABAergic system dysregulation, making benzodiazepines the gold standard treatment. These drugs modulate GABA receptors, with lorazepam being the most commonly used, typically in doses ranging from 6 to 24 mg[35]. Diagnostic tests, such as the lorazepam test, can help clarify the diagnosis. Lorazepam, a nonselective positive allosteric modulator of GABA-A receptors, is an effective and widely available diagnostic tool. It may be administered intravenously (1-2 mg), intramuscularly (1-2 mg), or orally (2 mg), although oral administration is slower and may be less practical for hyperkinetic or hypokinetic patients[33,35]. A positive response to the lorazepam challenge test, typically defined as a 50% reduction in catatonic signs on a standardized scale, supports the diagnosis of catatonia but is not completely specific. A strong response on the 1st day often predicts overall success of lorazepam treatment (Table 4)[33,36,37].

Table 4. Lorazepam challenge

Step	Action	Details
Baseline assessment	Assess catatonic features	Use a standardized instrument
Lorazepam administration	Administer lorazepam	1-2 mg IV 1-2 mg IM 2 mg orally
Reassessment	Reassess catatonic features	At 5 min (IV) At 15 min (IM) At 30 min (oral)
Response evaluation	Determine positive response	50% reduction in standardized catatonia score
Follow-up	If no positive response	Consider another lorazepam challenge (preferably parenteral) and reassess

In children, the lorazepam challenge has been described, and it should be initiated when the pediatric catatonia rating scale or the BFCRS indicate four or more positive items with a score above zero. If autonomic instability is present, malignant catatonia must be suspected. This severe condition carries a mortality rate of 10-20% if untreated. In such cases, intensive care management and urgent consideration of ECT are necessary[38]. In the largest study of lorazepam testing for pediatric catatonia, Luccarelli et al. evaluated 54 pediatric patients[39]. A significant response was observed, with mean BFCRS scores decreasing from 16.6 ± 6.1 to 9.5 ± 5.3 following lorazepam administration (Hedges' g = 1.20; 95% confidence interval: 0.85-1.55). Dosages ranged from 0.5 to 2 mg, with a mean of 0.029 mg/kg. Higher doses required close monitoring for potential side effects such as excessive sedation, paradoxical disinhibition, or glycol toxicity. A refractory or partial response to benzodiazepines is more common in patients with comorbid neurodevelopmental disorders or chronic catatonia[39].

The British Association for Psychopharmacology (BAP) recommends benzodiazepines as first-line treatment for catatonia, with several routes of administration available, including oral, sublingual, intramuscular, and intravenous. The choice of route should be individualized to the patient's clinical context and drug

availability. Lorazepam is generally the benzodiazepine of choice for treating catatonia. In some cases, high doses exceeding the usual prescribed range may be necessary to achieve optimal symptom relief. A trial of treatment is considered appropriate when catatonia has significantly improved, dose titration has been stopped due to side effects, or a daily dose of at least 16 mg has been reached.

Benzodiazepines should be tapered gradually to avoid withdrawal and minimize long-term risks. The tapering pace should balance therapeutic benefit with the risk of rapid reduction. If catatonic symptoms return, underlying conditions must be reassessed and treated. Zolpidem is also effective, particularly in lorazepam- or ECT-resistant cases, with a typical dose of 10 mg (or 5 mg for older adults) and effects lasting 3-6 h[33,40].

ECT

ECT has been used since the middle of the last century and is effective in cases with poor response to pharmacological treatments, with response rates of 80-100%, although efficacy is lower in cases where treatment is delayed. For patients with catatonia who see little or no benefit from benzodiazepine treatment, ECT remains the gold standard[41]. ECT might be considered earlier in the treatment algorithm if the situation is emergent, such as malignant catatonia. Response rates generally range from 80% to 100%.

Its high response rates warrant strong consideration in psychiatric and medical units where it is available. While benzodiazepines are first-line, delays in recognizing catatonia or initiating treatment may worsen outcomes, emphasizing the need for early intervention. In settings with access to ECT, its integration into treatment protocols (especially in cases of malignant or benzodiazepine-resistant catatonia) may improve outcomes.

Better outcomes are associated with younger age, autonomic dysfunction, and greater initial severity, while prolonged illness and neurological conditions may reduce responsiveness. If ECT fails, an underlying neurological disorder should be considered. Catatonia linked to mood disorders generally responds better to ECT than schizophrenia-related cases, though combining ECT with clozapine may improve outcomes. Variability in treatment response highlights the need for individualized care. The rapid response to ECT and benzodiazepines suggests catatonia may reflect a shared neurological endpoint involving maladaptive hyperexcitability, with ECT modulating cortical excitability and disrupting pathological synaptic activity[42].

There is no standardized ECT protocol for catatonia. Most evidence supports a robust approach with bitemporal, short pulse width, and high intensity stimulus ECT. Alternative locations, such as right unilateral stimulation or ultra-brief pulsatile stimulation, have been used, but their efficacy compared to bitemporal ECT remains unclear. Cognitive side effects are not usually a priority in cases of life-threatening catatonia. ECT is typically administered 3 times/week, with increased frequency in malignant catatonia. Adjustments to stimulus intensity are made if the duration of the seizure response is < 25 s.

ECT is effective in children, adolescents, and older adults, with response rates of approximately 75% in younger populations. While its use in pediatric populations requires careful consideration, available evidence supports its safety and efficacy in severe cases of catatonia[43].

Pediatric ECT is indicated for malignant or treatment-resistant catatonia. Bitemporal electrode placement is recommended, with sessions typically conducted 2-3 times/week. However, higher frequency may be required in some cases[38].

Other treatments

When first-line treatments for catatonia are unavailable or ineffective, the BAP guidelines recommend alternatives such as NMDAR antagonists (amantadine or memantine). Other options include levodopa, dopamine agonists, mood stabilizers (e.g., carbamazepine, valproate, and topiramate), or second-generation antipsychotics (SGAs). Antipsychotics should be avoided unless treating an underlying psychotic disorder, and used cautiously due to the risk of NMS. SGAs, especially clozapine, are preferred if antipsychotics are necessary. Caution is advised in patients with low serum iron or NMS history, particularly in pediatric cases, where gradual introduction and concurrent benzodiazepine use are recommended[44,45].

Future research directions

Future research on catatonia should focus on the following areas: (1) genetic and epigenetic studies, including genome-wide association analyses, to identify susceptibility loci and molecular mechanisms underpinning catatonic syndromes across populations. (2) Development of rapid diagnostic and screening tools validated for both pediatric and adult

populations, such as the Catatonia Quick Screen, to enable earlier detection in diverse clinical settings. (3) Multimodal neurobiological research, combining functional imaging (fMRI, PET) with biomarker analysis and genetic data, to map the neural circuits and biochemical pathways involved. (4) Rigorous evaluation of treatment strategies, including randomized trials of benzodiazepines, NMDA antagonists, Z-drugs, antipsychotics, and non-pharmacological interventions (e.g., TMS), with attention to safety and efficacy in children and adults. (5) Strengthened interdisciplinary collaboration – involving psychiatrists, neurologists, pediatricians, psychologists, and allied health professionals – to develop comprehensive care models, improve training, and promote timely recognition across all clinical settings.

Conclusion

This review highlights the heterogeneous presentation of catatonia, emphasizing the importance of recognizing clinical signs for optimal treatment. Early intervention with benzodiazepines or ECT is critical to improving outcomes. Clinicians, in general, must be sensitized to its varied manifestations to reduce diagnostic delays and prevent complications.

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Conflicts of interest

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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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