Review Article Brain Conflux

Advancing Precision Medicine through Polygenic Risk Scores: From Statistical Innovation to Clinical Implementation

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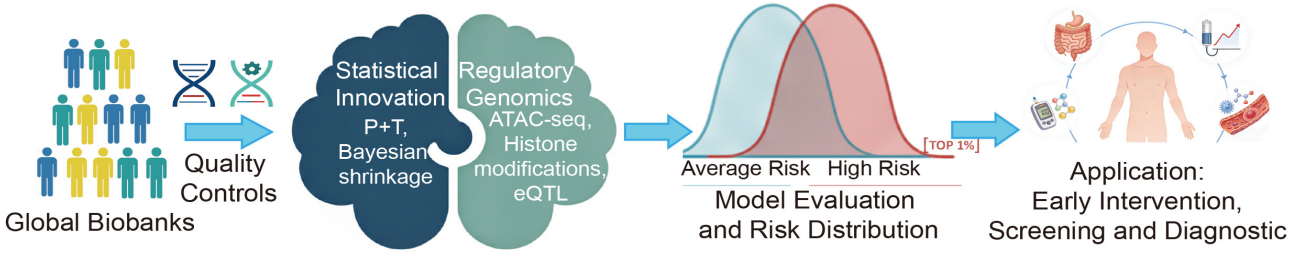
Graphical Abstract



https://doi.org/10.71321/ptbkr794

Review Article

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Advancing Precision Medicine through Polygenic Risk Scores: From Statistical Innovation to Clinical Implementation

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Received: 2025-11-23 | Accepted: 2026-03-01 | Published online: 2026-03-17

Abstract

The polygenic risk scores (PRS) have emerged as a transformative approach for quantifying inherited predisposition to complex diseases, leveraging the unprecedented expansion of genome-wide association studies (GWAS) and advances in statistical genetics. By aggregating the marginal effects of millions of common variants, PRS provide a single metric of genetic liability that can achieve predictive performance comparable to traditional clinical risk factors. Current methodologies are undergoing a paradigm shift, moving beyond simple linear additive models to incorporate complex linkage disequilibrium (LD) structures, multi-ancestry frameworks, and functional genomic landscapes. In particular, the integration of regulatory annotations, including expression quantitative trait loci (eQTL), chromatin accessibility, and cell-type-specific enhancers, has enhanced both the biological interpretability and predictive robustness of these scores.

This review synthesizes the rapid methodological evolution of PRS, encompassing Bayesian shrinkage frameworks, machine learning algorithms, and functionally informed strategies designed to mitigate the persistent Eurocentric biases in current datasets. We critically evaluate the evidence supporting the integration of PRS into clinical workflows, focusing on cardiovascular diseases, oncology, and neuropsychiatric disorders, where genetic stratification can enhance preventive interventions and diagnostic precision. Despite this progress, we identify significant challenges to widespread adoption, including the reduced portability of scores across diverse populations, the lack of standardized clinical thresholds, and complex ethical considerations related to health equity.

Finally, we propose a multidisciplinary roadmap for the future of PRS, emphasizing the necessity of global biobank diversity, dynamic risk modeling that incorporates temporal and environmental factors, and the seamless integration of genomic insights into electronic health records. Collectively, these advancements are essential for transitioning PRS from a powerful research tool into an equitable and actionable component of the precision medicine toolkit.

Keywords: Polygenic risk scores; Genome-wide association studies; Precision medicine; Clinical implementation

Introduction

The trajectory of human genetics has been fundamentally reshaped by the success of genome-wide association studies (GWAS), which have elucidated the polygenic architecture of complex traits [1]. It is now well established that the genetic liability for most common diseases is not driven by a single high-effect variant but rather by the cumulative contribution of thousands of variants, each exerting subtle effects. Polygenic risk scores (PRS) as a core tool for measuring the genetic susceptibility to complex diseases have played an important role in genomic research [2]. By distilling genome-wide summary statistics into a personalized risk profiles, PRS offer a unique opportunity to identify individuals at the extreme tails of the risk distribution, where the genetic burden may rival the impact of rare, high-penetrance mutations, as observed in conditions such as coronary artery disease (CAD), breast cancer, and type 2 diabetes (T2D) [3-5].

However, the surge of interest in PRS has simultaneously revealed critical systemic bottlenecks that hinder their wide-

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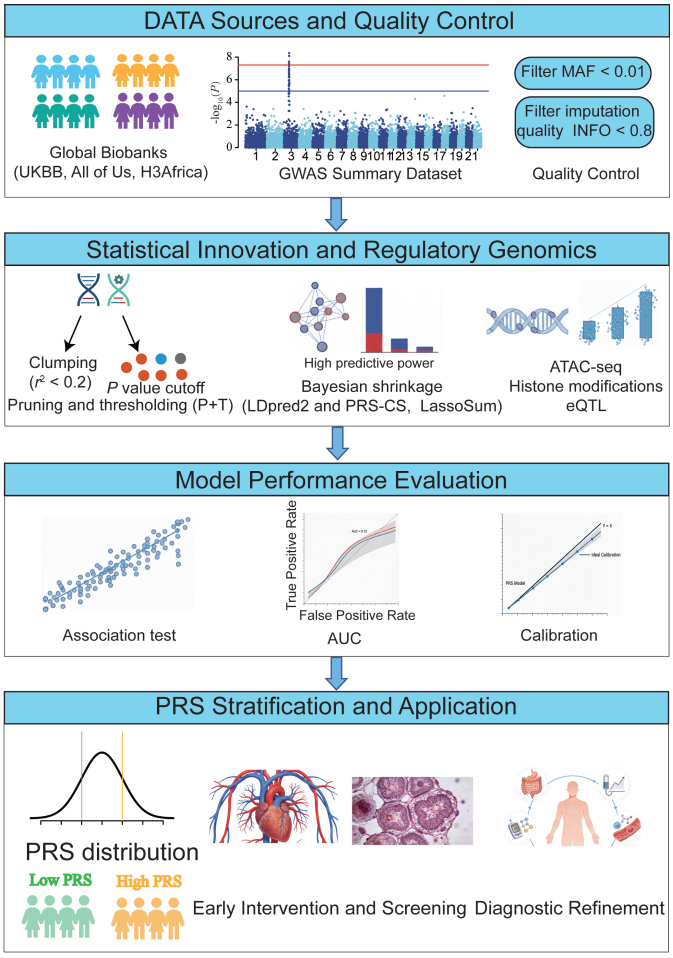
spread clinical adoption [6]. Primarily, the predictive accuracy of PRS is inextricably linked to the ancestral composition of the discovery GWAS. The current genomic landscape remains profoundly Eurocentric, creating a portability crisis in which scores developed in European cohorts exhibit diminished performance and, in some cases, complete failure in non-European populations [7-9]. This ascertainment bias not only limits the global utility of genomic medicine but also risks exacerbating existing health disparities. Furthermore, while early PRS relied on simple clumping and thresholding heuristics, the field now demands more statistically rigorous frameworks. Modern Bayesian and machine learning methodologies, such as LDpred2 and SBayesR, have refined effect-size estimation by accounting for complex linkage disequilibrium (LD) structures [10-12]. However, their transition from computational benchmarks to standardized clinical tools remains fragmented.

A parallel revolution in regulatory genomics is now providing the missing link between statistical correlation and biological causation. By integrating multiple omics layers, including expression quantitative trait loci (eQTL), chromatin accessibility profiles, and single-cell regulatory maps, researchers are advancing toward functionally informed PRS [13-14]. These approaches prioritize variants within causal regulatory elements, thereby enhancing signal-to-noise ratios and potentially improving cross-population portability. Beyond mere prediction, this integration facilitates a mechanistic understanding of how polygenic risk converges on specific tissue types and biological pathways [15].

Despite significant technical progress, the clinical implementation of PRS remains at a crossroads. Formidable challenges persist in establishing clinically actionable risk thresholds, calibrating scores for diverse healthcare settings, and effectively communicating probabilistic risks to both providers and patients [16-18]. As the field advances toward a more mature phase of genomics-informed healthcare, there is a pressing need for frameworks that are not only statistically robust but also biologically grounded and ethically equitable [19].

This review offers a comprehensive synthesis of the PRS landscape, tracing its progression from methodological innovation to clinical application. We place particular emphasis on three key pillars: resolving cross-ancestry biases, integrating functional genomics to enhance interpretability, and developing pragmatic strategies required to embed these scores into real-world clinical decision-support systems (Figure 1).

Figure 1. The construction and clinical translation of polygenic risk scores.



Construction of Polygenic Risk Scores

The architecture of a PRS represents a synthesis of genomic discovery and statistical refinement. For each individual, the PRS is computed by summing all SNPs, each weighted by its corresponding effect size. PRS is calculated across a range of *P* value thresholds, such as P_T = 0.0001, 0.0002, ..., 0.05, ..., 0.1, ..., 0.5. The *P* value threshold, P_T, that yields the highest R^2 is considered the most predictive cutoff [20]. While the foundational principle, aggregating weighted risk alleles, is straightforward, the transition from raw GWAS summary statistics to a clinically predictive tool involves complex modeling to account for LD, allelic heterogeneity, and ancestral architecture [11, 21]. This section delineates the essential components of PRS construction, highlighting the shift from heuristic-based filtering to sophisticated probabilistic frameworks.

Data Sources and Quality Control

The accuracy of any PRS is inherently limited by the quality of its underlying GWAS. Modern discovery datasets increasingly utilize large-scale biobanks, such as the UK Biobank, FinnGen, and All of Us, which provide the high-resolution genetic maps necessary for dissecting polygenic traits [22-23]. However, the effectiveness of PRS depends on both statistical power and ancestral alignment. Rigorous quality control (QC) remains essential to prevent the accumulation of statistical noise. Rare variants with a minor allele frequency (MAF) below 0.01 are traditionally excluded due to unstable effect size estimates, although they represent a promising frontier for sequencing-based PRS [24-25]. Additionally, stringent filtering for imputation quality (such as INFO score > 0.8) is critical, especially in non-European populations where reference panels are often less optimized, resulting in increased measurement error and reduced predictive power [26].

Statistical Weighting and LD Modeling

A central challenge in PRS construction is the deconvolution of LD structures. Because causal variants are often concealed within large blocks of co-inherited SNPs, simple GWAS effect sizes are inherently confounded by the surrounding LD landscape [27].

The first method is heuristic pruning and thresholding (P+T).

Early PRS methodologies relied on clumping (r^2 < 0.2) and P-value thresholding. While computationally efficient, these approaches often discard informative independent signals and fail to capture the cumulative contribution of sub-significant loci, which are critical for highly polygenic traits. The second method involves Bayesian shrinkage and joint modeling. To overcome the limitations of P+T, contemporary frameworks employ Bayesian shrinkage techniques (such as LDpred2 and PRS-CS) or penalized regression methods (such as Lasso-Sum) [28]. These methods utilize external LD reference panels to model the posterior distribution of effect sizes, effectively shrinking the effects of SNPs in high-LD regions to mitigate overestimation. These models significantly outperform P+T in capturing the heritability of complex phenotypes [10, 29].

The Role of Functional Priors

Perhaps the most significant advancement in PRS construction is the shift from biology-agnostic models to functionally informed frameworks. Instead of treating all SNPs equally, methods such as PolyFun-PRS and AnnoPred utilize functional genomic data, including chromatin accessibility (ATAC-seq), histone modifications (such as H3K27ac), and eQTL profiles, to assign informed priors to genetic variants [30-31]. By prioritizing variants located within cell-type-specific regulatory elements, these models not only improve predictive accuracy but also establish a mechanistic link between non-coding variation and disease pathophysiology [32].

Evaluating Model Performance

The validation of a PRS requires more than a simple correlation. It necessitates a multidimensional assessment, including: (1) Discrimination, evaluated using the area under the receiver operating characteristic curve (AUROC) or the C-index for time-to-event data [33]. (2) Calibration, which ensures that the predicted probability of disease aligns with the observed incidence in independent cohorts [34]. (3) Incremental value, which determines whether the PRS provide additional predictive power beyond established clinical risk factors such as age, sex, BMI, and lipid profiles [35].

Clinical Applications: From Risk Prediction to Precision Intervention

Despite promising predictive performance, the real-world clinical benefit of PRS-guided interventions remains under active investigation, and large-scale prospective trials are still limited. The clinical translation of PRS represents a shift toward a genomics-first approach in preventative medicine. While traditional clinical risk factors, such as blood pressure, lipid profiles, family history, reflect current physiological states, PRS provide a stable, lifelong measure of innate genetic liability [36]. This section evaluates the evidence supporting PRS across major disease domains, emphasizing its role in enhancing risk stratification and guiding personalized clinical decision-support systems.

Firstly, cardiovascular disease, particularly CAD, serves as the prototype for PRS-informed healthcare [37]. Large-scale biobank studies have demonstrated that individuals in the top 0.5% to 1% of the PRS distribution have a disease risk comparable to those with monogenic mutations, such as familial hypercholesterolemia [38]. Importantly, PRS can identify this high-risk group among individuals with normal LDL-C levels, who would otherwise be missed by traditional screening protocols [39-40]. The clinical utility of CAD PRS is further supported by evidence showing that individuals at high genetic risk derive a greater absolute benefit from statin therapy, regardless of their baseline clinical risk [41]. This establishes a clear pathway for precision prevention, where genetic markers can justify earlier or more intensive pharmacological interventions.

In oncology, PRS are increasingly integrated into risk-stratification models to optimize the timing and frequency of cancer screening. Individuals with high PRS (top 1%) exhibit a 4- to 6-fold increased risk of breast cancer, comparable to that conferred by moderate-penetrance variants [16]. Integrating PRS with traditional models has been shown to refine the recommended starting age for mammography, potentially reducing the burden of over-screening in low-risk individuals while intensifying surveillance for those who are genetically vulnerable [4, 42]. A significant advancement in oncology is the use of polygenic modulation to better understand monogenic risk. PRS can explain the incomplete penetrance of high-risk variants, such as *BRCA1* and *BRCA2*, providing a more nuanced and individualized risk estimate that is essential for surgical counseling and long-term surveillance [43].

When referring to T2D and obesity, PRS provide early-life insights that precede the manifestation of metabolic biomarkers [44]. PRS can predict T2D risk decades before the onset of hyperglycemia. Evidence from the Diabetes Prevention Program suggests that individuals with a high genetic risk may experience enhanced benefits from intensive lifestyle modifications or early metformin intervention, indicating the potential for genetics-informed lifestyle coaching [39, 45].

Despite challenges posed by phenotypic heterogeneity, PRS provide critical support in psychiatric diagnostics and neurodegenerative risk assessment [46]. In psychiatry, PRS have shown promise in differentiating between schizophrenia and bipolar disorder during early-stage psychosis, where clinical presentations often overlap [47]. The transition from static PRS to polygenic hazard scores (PHS), which incorporate age-dependent risk, has revolutionized the prediction of Alzheimer's disease (AD) onset [48]. PHS correlate strongly with cerebrospinal fluid (CSF) biomarkers, such as amyloid-β and tau, and brain atrophy, providing a valuable tool for stratifying participants in clinical trials of disease-modifying therapies [49-50].

Beyond risk prediction, PRS are increasingly used to refine the interpretation of rare variants and to predict drug responses [51]. Recent evidence suggests that the clinical severity of many monogenic conditions, such as cardiomyopathies, is significantly influenced by the polygenic background, supporting a polygenic modifier model that improves the accuracy of variant classification [52].

Challenges and Limitations: Navigating the Obstacles to Clinical Utility

Despite the rapid advancement of PRS methodologies, several fundamental barriers, ranging from ancestral disparities to methodological opacity, must be addressed to ensure their safe and equitable deployment. These challenges can be categorized into three critical dimensions: including ancestral portability, biological complexity, and implementation ethics (Table 1).

When considering ancestral portability, the most significant

limitation of current PRS is the Eurocentric ascertainment bias. Since the majority of discovery GWAS are conducted in individuals of European descent, the resulting scores often fail to generalize to global populations [7-8]. For example, predictive performance can decrease substantially in non-European cohorts, such as a 4-fold reduction in CAD-PRS accuracy in African populations. This decline is driven by divergent LD patterns, differences in allele frequencies, and heterogeneous gene-environment interactions [53]. Applying these biased scores in clinical settings without cross-ancestry calibration risks exacerbating existing health disparities, effectively creating a genomic divide between populations [54].

Regarding biological complexity, although Bayesian and machine learning models have enhanced statistical calibration, significant gaps remain in fully capturing the genetic architecture of complex traits. Current PRS typically account for only a fraction of the narrow-sense heritability [55]. The missing heritability is likely hidden in rare variants, structural variations, and complex epistatic interactions that are inadequately captured by SNP-based microarrays [56-57]. Traditional PRS provide only a snapshot of genetic risk and often overlook the temporal dynamics of disease, such as age-dependent penetrance, and the longitudinal accumulation of risk influenced by changing environmental exposures [58].

Regarding implementation ethics, the transition from a statistical probability to a clinical diagnosis involves complex sociotechnical challenges. PRS are inherently probabilistic, not deterministic [59]. Misinterpreting a high-percentile score as an inevitable diagnosis can lead to psychological distress or unnecessary medical procedures, while a low score may foster a false sense of security [16-17]. Currently, there is a paucity of standardized frameworks for clinical validation, reporting, and integration into electronic health records. Without rigorous regulatory oversight and consensus on risk thresholds, the utility of PRS remains inconsistent across different healthcare systems [60].

Future Directions: A Roadmap to Next-Generation Precision Medicine

To transition PRS from an experimental metric to a cornerstone of genomic medicine, the field must undergo a multidisciplinary evolution characterized by biological depth, algorithmic transparency, and global inclusivity.

The first topic concerns decolonizing genomics and promoting multi-ancestry innovation. The priority for the next decade should be the globalization of genomic discovery. Initiatives such as H3Africa, the Mexico City Prospective Study, and the All of Us are essential for building diverse reference panels [61-62]. Future algorithms, including next-generation PRS-CSx, must better leverage shared genetic architectures while explicitly modeling population-specific LD and environmental contexts to achieve equitable portability [63].

The second future direction involves functionally informed and multi-omic integration. We anticipate a shift from biology-agnostic SNPs to mechanistically grounded risk profiles. Integrating single-cell regulatory maps and spatial transcriptomics will enable PRS to prioritize variants with high functional impact in disease-relevant tissues, such as microglia in AD or cardiomyocytes in CAD [64-65]. Combining PRS with real-time proteomic and metabolomic data will facilitate a dynamic risk framework that captures the interplay between stable genetic liability and fluctuating biological states [66].

The third area concerns deep learning and AI. While linear additive models have traditionally been the foundation of PRS, deep learning approaches, such as graph neural networks and transformers, offer the potential to capture non-linear epistatic effects and complex structural variations [67-68]. However, the emphasis must remain on explainable AI to ensure that these black-box models provide clinicians with interpretable biological pathways rather than merely a numerical score [69].

The ultimate goal is the seamless integration of PRS into real-world clinical decision-support systems. The future development of PRS will focus on dynamic and multidisciplinary integration, combining longitudinal environmental data, multi-omics information, and interpretable AI technologies to achieve individualized life cycle risk assessment [70]. Developing international guidelines for the polygenic risk reporting, comparable to standard lipid panels, is essential for clinician education and patient empowerment [71].

Table 1. Challenges and Solutions in the Clinical Application of PRS

Dimension	Key Challenges and Bottlenecks	Proposed Strategic Solutions
Equity and Diversity	Eurocentric ascertainment bias: attenuated portability in non-European populations due to divergent LD and allele frequencies.	Expand global biobank diversity and implement multi-ancestry Bayesian frameworks.
Biological Depth	Black box additivity: additive models ignore non-linear epistasis, gene-environment interactions, and rare variants.	Integrate single-cell regulatory maps and proteomic data and utilize explainable AI to map risk to specific biological pathways.
Clinical Utility	Lack of standardization: absence of consensus on risk thresholds, reporting formats.	Establish international polygenic risk reporting standards.
Temporal Dynamics	Static risk snapshot: conventional PRS fail to account for age-dependent penetrance and cumulative environmental risk.	Develop polygenic hazard scores that integrate age and biomarkers into dynamic, life-course risk trajectories.
Ethical and Social	Psychosocial impact: risk of fatalism, misinterpretation of probabilistic data, and insurance discrimination.	Develop genetic counseling toolkits and implement regulatory frameworks to protect genomic privacy and prevent bias.

Conclusion and Future Perspectives

PRS have catalyzed a paradigm shift in genomic medicine, evolving from theoretical constructs into quantitative tools capable of deciphering the inherited architecture of complex diseases [72]. By aggregating signals from millions of common variants, PRS provide a unique metric of genetic liability that complements traditional clinical biomarkers, offering insights into personalized disease prevention and biologically informed diagnostics [73]. Over the past decade, this field has experienced exponential growth, driven by the integration of functional genomics, pleiotropic frameworks, and machine learning methodologies, all of which have progressively enhanced both the predictive accuracy and the mechanistic interpretability of these scores [74-75].

However, the path toward widespread clinical adoption is marked by significant systemic challenges. PRS remain probabilistic estimates rather than definitive diagnoses, and their predictive capacity is currently limited by the missing heritability contained in rare variants, structural variations, and complex interactions [57]. Perhaps most critically, the Eurocentric ascertainment bias present in existing genomic datasets constitutes a major bottleneck. Without the rigorous development of multi-ancestry reference panels and trans-ancestry modeling, the clinical implementation of PRS risks inadvertently exacerbating global health disparities [7, 53]. Furthermore, transitioning to real-world healthcare applications requires addressing complex ethical and regulatory challenges, including standardized risk communication, data privacy, and the establishment of robust clinical decision-support systems [16, 18].

The next frontier of PRS lies in their dynamic and multidisciplinary integration. By harnessing longitudinal environmental data, multi-omic layers, and explainable AI, the field is advancing toward life-course risk trajectories, dynamic assessments that evolve as an individual age [76]. Achieving this vision requires a concerted effort to decolonize genomics, ensuring that the benefits of precision medicine are accessible across all ancestral backgrounds.

In conclusion, PRS represent a fundamental pillar of the next generation of precision medicine. Their transformative potential, however, depends on a synergistic commitment to methodological rigor, clinical utility, and social equity. Only through close interdisciplinary collaboration among geneticists, clinicians, bioinformaticians, and policymakers can we bridge the gap between genomic discovery and impactful public health outcomes, ultimately materializing the promise of polygenic prediction into a global clinical reality.

Abbreviations

PRS: polygenic risk scores; GWAS: genome-wide association studies; eQTL: expression quantitative trait loci; CAD: coronary artery disease; T2D: type 2 diabetes; LD: linkage disequilibrium; MAF: minor allele frequency; HWE: hardy-weinberg equilibrium; CVD: cardiovascular diseases; FH: familial hypercholesterolemia; LDL: low-density lipoprotein; AD: alzheimer's disease; PHS: polygenic hazard scores; DPP: diabetes prevention program; EHR: electronic health records; MCI: mild cognitive impairment; AI: artificial intelligence.

Acknowledgements

This research was supported by Wenzhou Key Laboratory of Health Big Data and Translational Medicine.

Author Contributions

Tao Wang and Jun Li collected and analyzed the literature, and wrote the initial manuscript. Yinghao Yao and Xing Zheng made contributions to the study design, modifying the manuscript. All authors collected the literature and endorsed the manuscript's final version.

Funding Information

This work was supported by the General Project of Zhejiang Provincial Education Department (Y202559997).

Ethics Approval and Consent to Participate

Not Applicable.

Competing interests

The authors declare no competing interests.

Data availability

Not Applicable.

Reference

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A Case of Epstein-Barr Virus Encephalitis Misdiagnosed as Glioma

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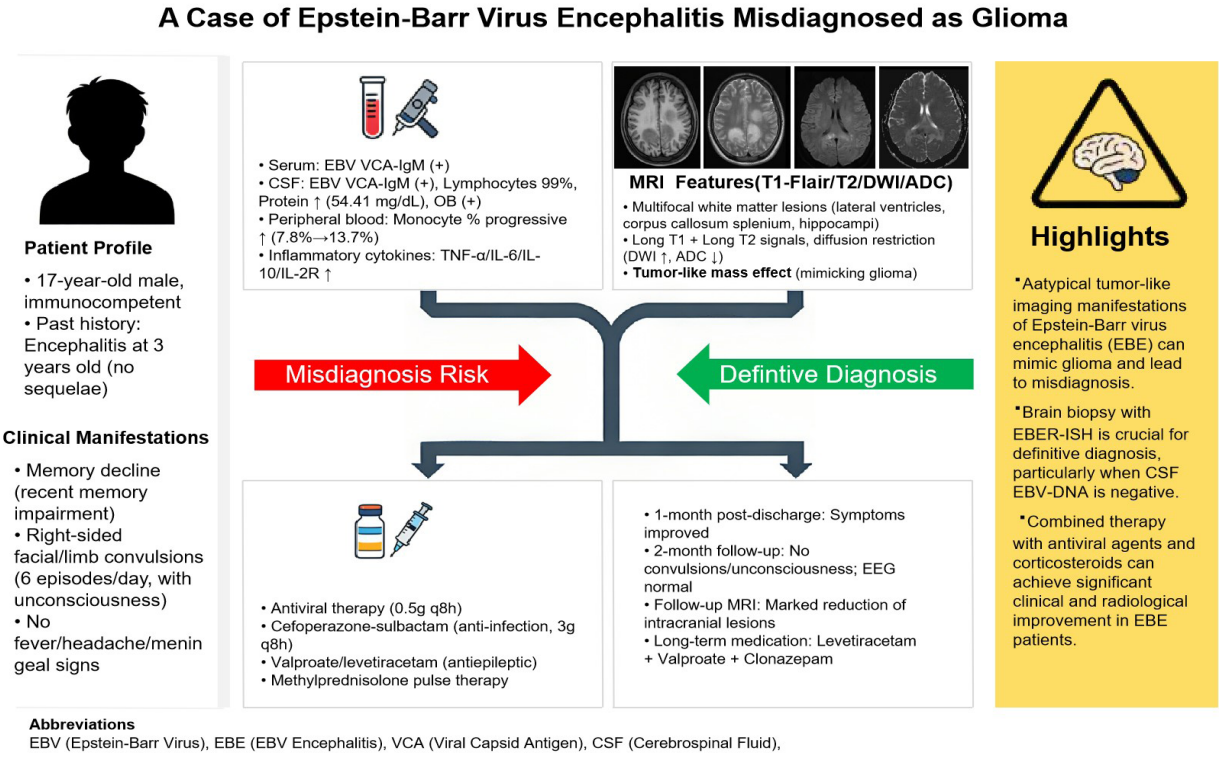
Graphical Abstract



https://doi.org/10.71321/c09vcg29

A Case of Epstein-Barr Virus Encephalitis Misdiagnosed as Glioma

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Received: 2025-10-05 | Accepted: 2025-10-21 | Published online: 2026-03-30

Abstract

Epstein-Barr virus (EBV) infection can cause central nervous system damage, primarily manifesting as encephalitis, with diverse imaging presentations. We report a case of an EBV-infected patient who presented clinically with cognitive impairment and limb convulsions. Serum and cerebrospinal fluid tests were positive for EBV viral capsid antigen IgM. Cranial MRI revealed multifocal white matter lesions distributed along the lateral ventricles, demonstrating T1 and T2 hyperintensity with associated diffusion restriction in the involved areas, patchy enhancement, and a tumor-mimicking appearance with significant mass effect. Brain biopsy confirmed viral encephalitis. After treatment with antiviral agents and corticosteroids, the patient's symptoms improved. Follow-up cranial MRI one month later showed significant reduction of the lesions. In clinical practice, it is important to be alert to the tumor-like imaging manifestations of EBV encephalitis. Pathological biopsy of brain tissue plays a crucial role in distinguishing this condition from diseases such as glioma.

Keywords: Epstein-Barr Virus Encephalitis; Glioma; Brain biopsy; Tumor-like lesions

Introduction

Epstein-Barr virus (EBV) is a double-stranded DNA virus that is lymphotropic for humans and belongs to the gammaherpesvirus family (human herpesvirus 4). It is highly prevalent in the human population, with over 90% of adults testing positive for EBV antibodies [1]. Central nervous system damage caused by EBV infection, referred to as Epstein-Barr virus encephalitis (EBE), can manifest as encephalitis, meningitis, transverse myelitis, radiculitis, and Guillain-Barré syndrome (GBS), with meningoencephalitis being the most common presentation [2]. The clinical and imaging features of EBE are highly variable. This article reports a case of EBE presenting with cognitive impairment and tumor-like imaging characteristics, aiming to enhance recognition of the atypical manifestations of this disease.

Case presentation

A 17-year-old male student was admitted on April 1, 2025, due to memory decline for over two weeks and limb convulsions for 10 days. According to the patient's sister, the patient experienced a rapid decline in memory over two weeks prior without an obvious cause, predominantly affecting recent memory, accompanied by slowed responses. There was no fever, headache, dizziness, nausea, vomiting, loss of consciousness, limb convulsions, or incontinence. A cranial MRI plain scan plus enhancement performed at a local hospital revealed multiple intracranial space-occupying lesions. Ten days prior to admission, the patient experienced episodic right-sided facial and limb convulsions during a hospital visit, accompanied by loss of consciousness, with each episode lasting from 10 seconds to several minutes and occurring up to six times per day. The seizures persisted despite antiepileptic treatment. Since the onset of illness, the patient had poor appetite and sleep, but normal bowel and bladder function, with no significant changes in weight. The family reported a suspected history of acute gastroenteritis prior to the onset of symptoms. Past medical history included encephalitis at the age of three, with no specific details available and no sequelae reported. There were no remarkable findings in personal or family history, and no histo-

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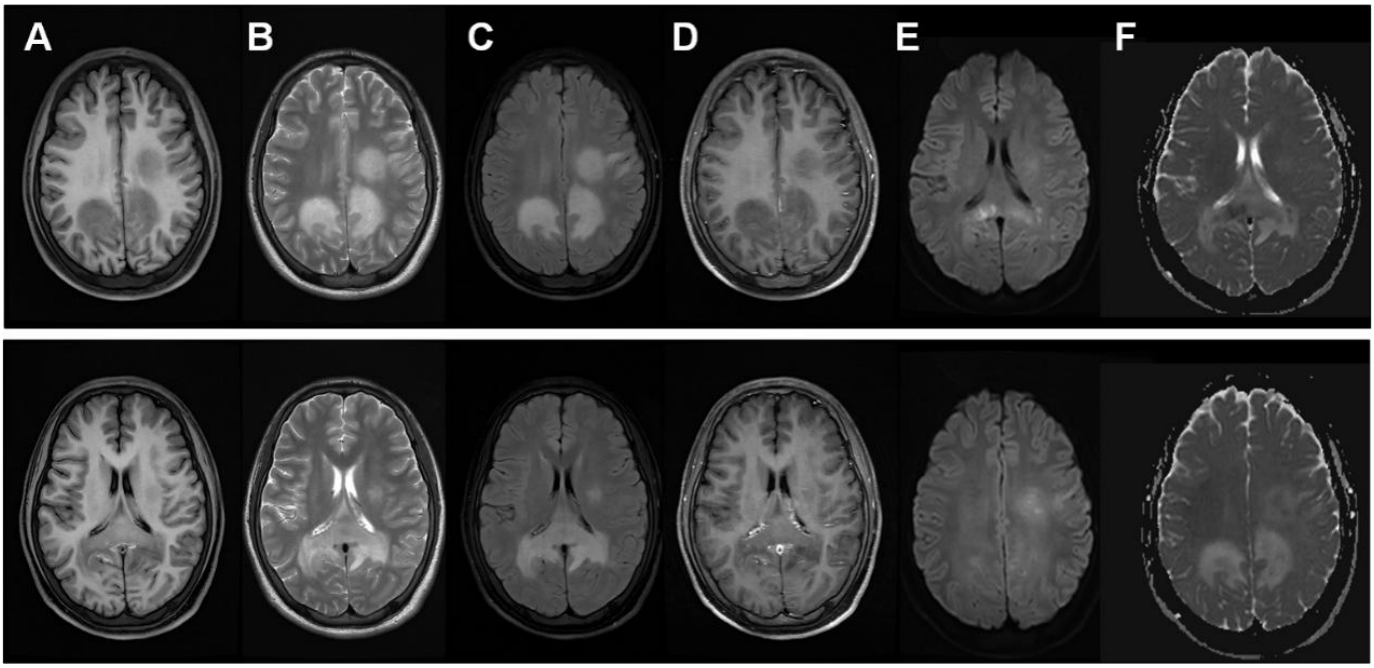
ry of mosquito bites, animal bites/scratches, or exposure to infectious diseases was reported. Physical Examination: Body temperature 36.2°C, pulse rate 76 bpm, respiratory rate 16 bpm, blood pressure 120/60 mmHg (1 mmHg = 0.133 kPa). The patient was conscious, oriented, but appeared slightly lethargic. Speech was clear, and he was cooperative during the examination. Higher cortical functions including comprehension, orientation, and calculation were grossly intact upon bedside testing. Significant memory impairment was noted, particularly affecting recent memory. Bilateral pupils were equal and round, approximately 3.0 mm in diameter, with normal light reflexes. Cranial nerve examination revealed no deficits. Muscle strength was grade 4 in all four limbs, with normal muscle tone. Deep tendon reflexes were graded 2+ bilaterally. Babinski signs were negative. The neck was supple, and no meningeal signs were observed. Accessory examination: Complete blood count revealed a progressive increase in the monocyte percentage: 7.8% (reference range 2.0%-11.0%) on 2025-03-23, 11.2% on 2025-04-08, and 13.7% on 2025-04-20. The corresponding absolute monocyte counts were 0.65×10^9 /L (reference range 0.14-0.74 $\times 10^9$ /L) on 2025-03-23, 1.11×10^9 /L on 2025-04-08, and 1.09×10^9 /L on 2025-04-20. Other hematological parameters were within normal limits. Procalcitonin was elevated at 0.093 ng/mL (reference range 0-0.05 ng/mL). Serum inflammatory cytokines showed elevated levels: TNF-α 17.2 pg/mL (reference range 0.0-8.1 pg/mL), IL-6 4.1 pg/mL (reference range 0.0-3.4 pg/mL), IL-10 11.5 pg/mL (reference range 0.0-9.1 pg/mL), and IL-2R 1449 U/mL (reference range 223-710 U/mL). Electrolyte panel indicated hypokalemia (potassium 3.1 mmol/L, reference range 3.50-4.9 mmol/L). Biochemistry tests revealed a blood glucose level of 3.29 mmol/L and elevated homocysteine at 22.7 μmol/L (reference value <15 μmol/L). Serology was positive for Epstein-Barr virus viral capsid antigen IgM (VCA-IgM) and positive for Cytomegalovirus IgG. A respiratory virus panel was positive for Haemophilus influenzae. Routine urinalysis, liver and kidney function, myocardial enzymes, C-reactive protein, erythrocyte sedimentation rate, immune markers and other three items were generally normal.

On March 22, 2025, a lumbar puncture was performed for cerebrospinal fluid (CSF) analysis. The CSF appeared colorless and transparent (opening pressure not documented). The white blood cell count was 8×10^6 /L (reference range 0-8 $\times 10^6$ /L), with a mononuclear cell predominance of 62.6%. CSF biochemistry showed an elevated protein level of 54.41 mg/dL (reference range 15-45 mg/dL), while glucose and chloride levels were within normal limits. Special CSF protein analysis revealed an elevated CSF albumin level of 0.4 mg/nL (reference range 0.0-0.15 mg/nL). CSF testing was positive for Epstein-Barr virus VCA-IgM. Both serum and CSF oligoclonal bands (OB) were positive. The intrathecal IgG synthesis rate was elevated at 11.32. Serological tests for anti-ganglioside antibodies (AGA), paraneoplastic syndrome-associated antibodies, and autoimmune antibodies were all negative. CSF cytology demonstrated a predominant lymphocytic population (99%). Cranial non-contrast and contrast-enhanced MRI revealed multiple abnormal signal intensities in the splenium of the corpus callosum, fornix, bilateral trigones of the lateral ventricles, bilateral hippocampi, and the left frontal lobe. Patchy enhancement was observed post-contrast administration (Figure 1). Cervical spine MRI showed no significant abnormalities. Following admission, the patient received supportive and symptomatic treatment, including antiviral therapy with acyclovir (0.50g every 8 hours), anti-infective therapy with cefoperazone-sulbactam (3g every 8 hours), and valproate sodium (0.5g twice daily). The patient's symptoms improved, although intermittent right-sided limb convulsions persisted.

Six days after admission, a brain biopsy was performed. Histo-

Figure 1. Cranial magnetic resonance imaging (MRI) findings on April 2, 2025. A-F show T1-FLAIR, T2, T2-FLAIR, T1-FLAIR+C, DWI, and ADC images, respectively. Irregular T1-hypointense and T2-hyperintense signals are seen in the splenium of the corpus callosum and bilateral centrum semiovale, appearing slightly hyperintense on T2-FLAIR. DWI shows mild hyperintensity with corresponding low ADC values. No significant enhancement is observed post-contrast.



pathological examination revealed mild glial hyperplasia, vascular dilation, and perivascular infiltration by numerous lymphocytes and monocytes. Immunohistochemistry results were as follows: H3K27Me3 (partially positive), H3K27M (negative), IDH1R132H (negative), ATRX (positive), P53 (focally positive), BRAF (negative), and Ki-67 proliferation index approximately 5%. Epstein-Barr virus-encoded small RNA in situ hybridization (EBER-ISH) was positive. Based on these collective findings, a diagnosis of EBE was established. Intravenous methylprednisolone pulse therapy (0.25g daily) was initiated. A repeat lumbar puncture four days later showed a CSF pressure of 130 mm-H_2O, with both cell count and protein level normalized to within reference ranges. Metagenomic next-generation sequencing of the CSF did not detect any pathogenic microorganisms.

One month after discharge, the patient had largely recovered, with only mild dysarthria and persistent involuntary twitching of the right upper limb remaining. At the two-month follow-up, there were no further episodes of limb convulsions or loss of consciousness. A repeat complete blood count showed a monocyte percentage of 10.7% with an absolute count of 0.64 × 10^9 /L. Follow-up cranial MRI demonstrated a significant reduction in the extent of the previous intracranial abnormal signals. The patient still has involuntary twitching of the right upper limb from time to time. The follow-up electroencephalogram showed normal electroencephalogram. At present, he has been taking levetiracetam, sodium valproate and clonazepam for a long time to control the symptoms.

Discussion

Epstein-Barr virus (EBV) exhibits a high seroprevalence in the general population and can infect individuals of all age groups without distinct seasonal variation. Human is the only host of EBV infection, mainly through the patient's oral saliva, but also through organ transplantation or blood transfusion. EBV infection is associated with a spectrum of conditions, including: (1) primary EBV infection, most commonly presenting as infectious mononucleosis (IM); (2) chronic active EBV infection (CAEBV); (3) EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH); (4) various malignancies, such as Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), nasoph-aryngeal carcinoma (NPC), gastric carcinoma, and post-transplant lymphoproliferative disorder (PTLD). Central nervous system involvement by EBV, designated as EBV encephalitis (EBE), is relatively uncommon, affecting approximately 0.4% to 7.5% of infected individuals [3]. Among them, age, underlying immunosuppression, and active peripheral EBV infection have been identified as independent risk factors for the development of EBE [4].

The pathogenesis of EBE remains incompletely understood. The prevailing hypothesis suggests that EBE primarily occurs via retrograde axonal transport of the virus along cranial nerves. However, recent studies have reported the existence of a lymphatic system within the brain that connects the subarachnoid space, venous sinuses, lymphatic vessels, and deep cervical lymph nodes. EBV may potentially exploit this pathway by invading the lymphatic system to gain access to the intracranial compartment, thereby facilitating the development of EBE [5]. Compared to other types of viral encephalitis, meningeal involvement is more frequently observed in EBE patients, implicating the disruption of the blood-brain barrier as a key mechanism in its pathogenesis [4]. Another critical mechanism is the immune response triggered by EBV within the central nervous system. EBV can stimulate B lymphocytes to produce a vast array of antibodies, including those targeting neuronal glycolipid components such as gangliosides. This can lead to widespread parenchymal damage and manifest as various demyelinating diseases, including acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome (GBS), and transverse myelitis [6]. Furthermore, studies have reported that reactivation of latent EBV under conditions of immunosuppression contributes to a range of CNS injuries. In the present case, the patient was immunocompetent. Serological and CSF findings were positive for EBV VCA-IgM, while antibodies for VCA-IgG and nuclear antigen (NA)-IgG were negative, and EBV-PCR on the brain biopsy specimen was positive. This profile is consistent with a primary EBV infection, indicating that the virus can directly invade the CNS to cause EBE. However, the patient showed positive cerebrospinal fluid OB test, increased IgG intrathecal synthesis, and multiple tumor-like lesions mainly in white matter on cranial MRI. We speculate that it may be related to immune-mediated neurological damage caused by EBV infection, and a variety of mechanisms were involved in the disease process of this patient.

The clinical manifestations of EBE encompass both systemic and neurological symptoms. Systemic symptoms are typically nonspecific, with headaches, fever, and gastrointestinal issues being the most common. Patients may also experience fatigue, pharyngitis, tonsillitis, myalgia, or urinary disorders. Neurological symptoms predominantly involve impaired consciousness levels and delirium. Other manifestations include cerebellar syndrome (characterized by unsteady gait and ataxia), secondary generalized tonic-clonic seizures, and meningeal irritation signs. Some patients may develop extrapyramidal symptoms or psychiatric disturbances, while cognitive impairment is the primary presentation in rare cases. The patient reported in this case initially presented with rapid memory decline, thereby expanding the known spectrum of EBE symptomatology. Primary EBV infection in immunocompetent individuals is typically asymptomatic or manifests as infectious mononucleosis (IM) [7]. Consistent with previous literature, although this patient did not exhibit significant leukocytosis, a notable increase in the monocyte percentage was observed, which gradually decreased over the course of the illness. However, the correlation between the kinetics of monocyte count and disease progression or prognosis has not been established in the current literature.

The routine cerebrospinal fluid examination results of EBE patients showed no significant difference from other types of viral encephalitis. The white blood cell count was slightly increased, among which 87% of patients showed lymphocyte increase with/without mild protein level increase [8]. The gold standard for EBE diagnosis is the detection of EBV-DNA positive in cerebrospinal fluid or brain biopsy, and the specific EB virus antibody test is the most powerful evidence for the diagnosis of EB virus encephalitis [9]. However, the positive rate of EBV-DNA in cerebrospinal fluid of EBE patients was about 87%, while most of the patients with EBV-DNA negative results were primary EBV infection patients [8]. The CSF analysis of this patient showed a mild increase in lymphocyte-dominated white blood cells with elevated protein levels. However, the EBV-DNA

test in the CSF was negative. The possible reasons are as follows: Firstly, the CSF was positive for EBV VCA-IgM while negative for VCA-IgG, indicating a primary EBV infection. Secondly, the lumbar puncture for EBV-DNA testing was performed after the initiation of antiviral therapy; the negative result may therefore be attributed to the timing of the test and a potential decrease in viral load following treatment. It is important to note that the detection of EBV-DNA in the CSF is not entirely specific for EBE, as it has also been associated with central nervous system lymphoproliferative disorders, particularly HIV-associated primary central nervous system lymphoma (PCNSL) [10] and post-transplant lymphoproliferative disorder (PTLD) [11]. This underscores the critical role of brain biopsy in achieving a definitive diagnosis. Previous literature has reported eight confirmed EBE cases where EBV was detected in brain tissue; notably, one of these patients also had a negative CSF EBV-DNA result. In our case, the diagnosis of EBE was ultimately confirmed by a positive Epstein-Barr virus-encoded RNA (EBER) in situ hybridization on brain biopsy tissue. The histopathological findings lacked features typical of glioma, lymphoproliferative disease, or ADEM, thereby solidifying the diagnosis of EBE.

Neuroimaging serves as a crucial diagnostic tool in EBE. Notably, studies indicate that over half of EBE patients show no abnormalities on cranial CT scans, yet abnormal findings emerge on MRI results. This highlights the critical role of cranial MRI in both diagnosis and treatment of EBE [8]. The location of EBE lesions is not significantly specific, and it is more likely to involve the cerebral hemisphere, basal ganglia, cerebellum, brainstem, thalamus and limbic system [12]. The patient's cranial MRI revealed multiple lesions centered around the lateral ventricle, showing T1 low signal, T2 high signal, diffusion restriction, low ADC image intensity, and normal FLAIR image intensity. Mild contrast enhancement was observed (Figure 1). However, some EBE cases exhibit MRI features similar to gliomas and lymphomas, which can easily lead to misdiagnosis in early stages.

The treatment of EBE remains primarily supportive. The Infectious Disease Society of America (IDSA) guidelines recommend empirical antiviral therapy for all suspected encephalitis patients (Grade A recommendation) [13]. However, acyclovir is only a recommended antiviral agent for herpes simplex encephalitis (Class I A). At present, empirical and specific antiviral treatments for EBE are not supported by large randomized controlled trials. When there is immune-mediated demyelinating disease of the nervous system and EBV-associated hemophagocytic syndrome, corticosteroids should be used. In addition to anti-inflammatory and cerebral edema reduction, they can also reduce neurological sequelae. However, the decision to initiate therapy must be guided by a clear clinical rationale, necessitating strict adherence to established indications due to the potential for adverse effects [14].

Abbreviations

ADEM: Acute Disseminated Encephalomyelitis; AGA: Anti-Ganglioside Antibodies; CAEBV: Chronic Active EBV Infection; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; EBE: Epstein-Barr Virus Encephalitis; EBER-ISH: EBV-encoded RNA In Situ Hybridization; EBV: Epstein-Barr Virus; EBV-HLH: EBV-associated Haemophagocytic Lymphohistiocytosis; GBS: Guillain-Barré Syndrome; HL: Hodgkin Lymphoma; IDSA: Infectious Diseases Society of America; IL: Interleukin; IM: Infectious Mononucleosis; NA: Nuclear Antigen; NHL: Non-Hodgkin Lymphoma; NPC: Nasopharyngeal Carcinoma; OB: Oligoclonal Bands; PCNSL: Primary Central Nervous System Lymphoma; PTLD: Post-transplant Lymphoproliferative Disorder; VCA: Viral Capsid Antigen.

Acknowledgements

None.

Author Contributions

Yinuo Liu collected and analyzed the case data and drafted the initial manuscript. Ru Liu critically revised the manuscript for important intellectual content, including its structure and key statements, and finalized the writing. All authors reviewed and approved the final manuscript.

Funding Information

Not Applicable.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for publication of this case report. The procedures were in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

Not Applicable.

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Review Article

Brain Conflux

Deep Brain Stimulation for Parkinson's Disease: A Comprehensive Review of Efficacy, Influencing Factors, and Future Directions

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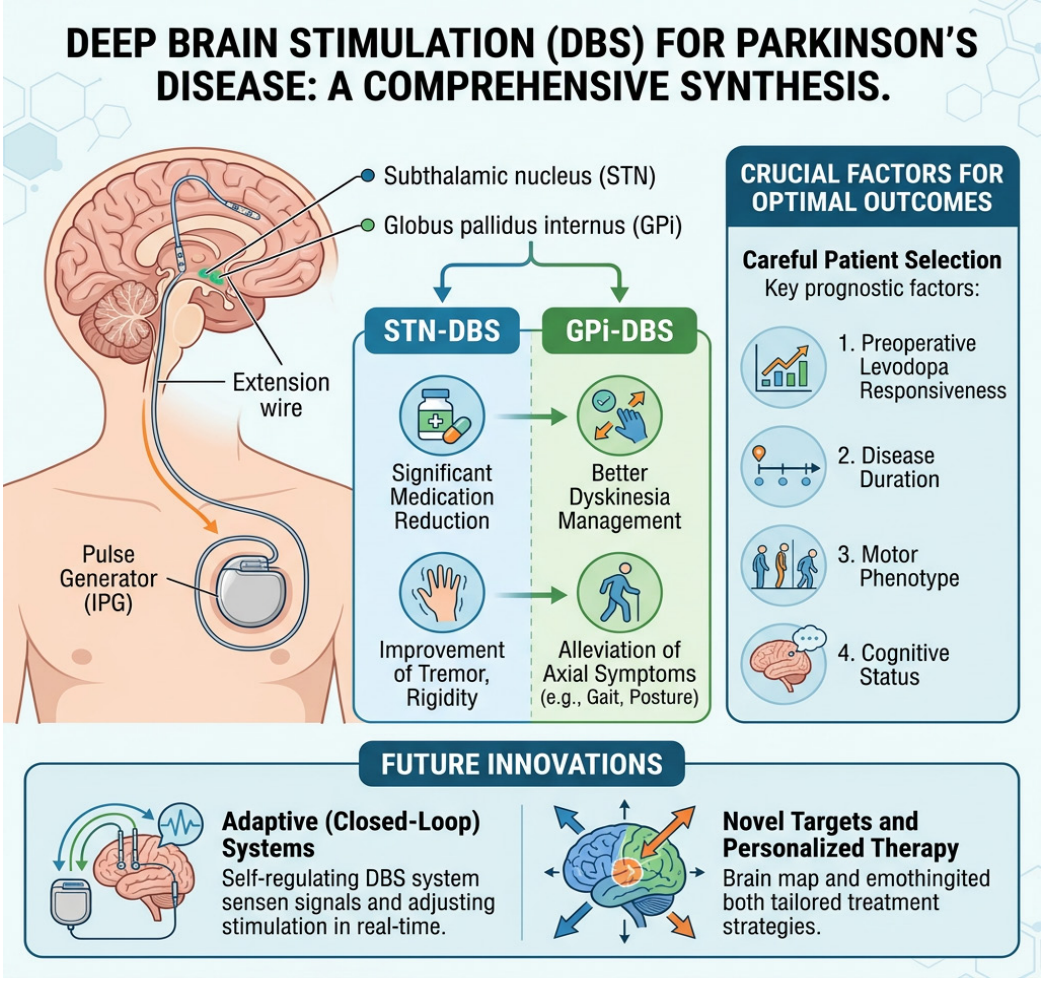
Graphical Abstract



https://doi.org/10.71321/qwdy0v52

Review Article Brain Conflux

Deep Brain Stimulation for Parkinson's Disease: A Comprehensive Review of Efficacy, Influencing Factors, and Future Directions

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Received: 2026-01-08 | Accepted: 2026-03-10 | Published online: 2026-03-30

Abstract

Deep Brain Stimulation (DBS) is a well-established surgical therapy for advanced Parkinson's disease (PD), effectively alleviating motor symptoms and complications associated with long-term levodopa treatment. This review provides a comprehensive synthesis of current evidence, analyzing the efficacy of the two primary targets, the subthalamic nucleus (STN) and the globus pallidus internus (GPi), on both motor and non-motor symptoms. While STN-DBS allows significant medication reduction and GPi-DBS may better manage dyskinesias and axial symptoms, outcomes are highly dependent on careful patient selection. Key prognostic factors include preoperative levodopa responsiveness, disease duration, motor phenotype, and cognitive status. The review also critically evaluates technological advancements, such as adaptive closed-loop systems and novel targets, which aim to personalize therapy and address treatment-resistant symptoms. Ultimately, DBS represents a transformative intervention whose success hinges on integrated clinical decision-making and continued innovation.

Keywords: Parkinson's Disease; Movement disorders; Deep brain stimulation; Review

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, imposing a significant and growing burden on global health systems [1-3]. Its core pathological hallmark is the degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to dopamine depletion in the striatum and consequent dysfunction of the cortico-basal ganglia-thalamocortical loops [4-6]. Clinically, PD manifests cardinal motor symptoms including tremor at rest, bradykinesia, rigidity, and, as the disease evolves, postural instability and gait disturbances [7-8]. The introduction of levodopa in the 1960s revolutionized PD treatment, providing remarkable symptomatic relief [9-11]. However, long-term levodopa therapy is inevitably complicated by the development of motor fluctuations (the "wearing-off" and "on-off" phenomena) and levodopa-induced dyskinesias (LID), which severely impair quality of life [10, 12-13].

For patients with these advanced, medication-refractory complications, Deep Brain Stimulation (DBS) has become a standard of care [14-16]. DBS involves the stereotactic implantation of electrodes into specific deep brain nuclei, connected to a subcutaneous implantable pulse generator that delivers continuous high-frequency electrical stimulation [17-19]. Since its widespread adoption in the late 1990s, DBS has demonstrated robust, long-term efficacy in ameliorating motor symptoms, reducing motor complications, and decreasing medication requirements [20-21]. The two primary and most validated targets for PD are the subthalamic nucleus (STN) and the globus pallidus internus (GPi), each with a distinct profile of benefits and potential side effects [22-23].

The objective of this review is to provide a comprehensive and systematic analysis of the current state of DBS for PD. It will synthesize evidence on the efficacy of DBS across the spectrum of motor and non-motor symptoms, delve into the critical patient and disease characteristics that predict surgical outcomes, and offer a critical evaluation of technological advancements and future research trajectories. By moving beyond a mere cataloging of effects to a nuanced discussion of mechanisms, predictors, and evolving paradigms, this review aims to consolidate knowledge for clinicians and researchers, and to identify key areas where further investigation is needed

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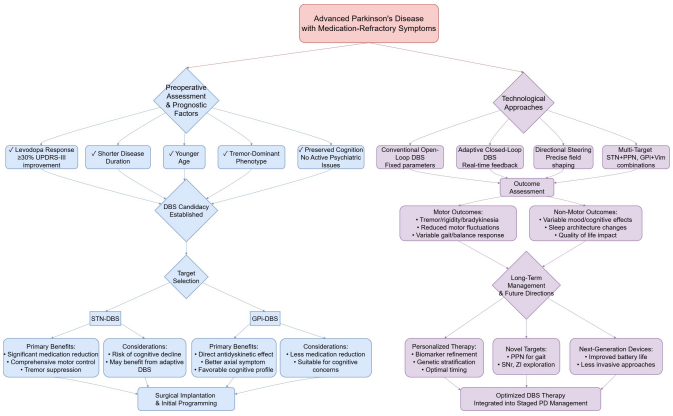
to optimize this powerful neuromodulation therapy (Figure 1).

Figure 1. Clinical decision pathway and technological evolution of deep brain stimulation (DBS) in Parkinson's disease (PD). This schematic summarizes the integrated process from patient selection to long-term management.
Patient Selection Criteria: highlights essential preoperative predictors of favorable outcome, including robust levodopa responsiveness, shorter disease duration, and younger age. Target Selection: contrasts the principal surgical targets as subthalamic nucleus (STN) and globus pallidus internus (GPi) based on their distinct benefit-risk profiles. Technological Approaches: outlines available stimulation strategies, from conventional open-loop to adaptive closed-loop and directional steering systems. Outcome Assessment: encompasses both motor and non-motor domains, reflecting the multidimensional impact of DBS. Future Directions: points toward personalized therapy, novel targets, and next-generation devices that aim to broaden efficacy and accessibility.



Efficacy of DBS on Motor Symptoms

The therapeutic impact of DBS on the major motor features of PD is well-documented and constitutes the primary rationale for its use [12, 24]. The magnitude of improvement, however, varies by symptoms and targets (Table 1).
To appreciate the differential effects of stimulating these two nuclei, a basic understanding of basal ganglia circuitry is essential. The basal ganglia are organized into parallel, functionally segregated loops that modulate cortical activity [4]. Within the motor loop, the striatum (putamen) receives cortical input and projects to the output nuclei as GPi and substantia nigra pars reticulata (SNr) via two main pathways: the direct and indirect pathways. The direct pathway, which facilitates movement, involves monosynaptic inhibitory projections from the striatum to the GPi/SNr. The indirect pathway, which suppresses unwanted movement, is a polysynaptic circuit involving the globus pallidus externus (GPe) and the STN [22].
The STN is a small, glutamatergic nucleus strategically positioned as a key driver of the indirect pathway. Excitatory output from the STN to the GPi/SNr serves to inhibit thalamocortical projections, thereby suppressing movement [36]. In PD, dopaminergic depletion in the striatum leads to overactivity of the STN, resulting in excessive excitatory drive to the GPi/SNr and pathological inhibition of the thalamus and cortex, which manifests as bradykinesia and rigidity [4]. In contrast, the GPi is the primary output nucleus of the basal ganglia, integrating inputs from both the direct and indirect pathways to send inhibitory signals to the thalamus [23]. In the parkinsonian state, GPi neurons exhibit abnormally high and burst-like firing rates, contributing to the same net inhibitory effect on thalamocortical circuits. Thus, while both nuclei become hyperactive in PD, the STN functions as a driving force within the indirect pathway, whereas the GPi serves as a final common output. This distinction as STN acts modulator of network drive and GPi as a regulator of final output provides a neurobiological rationale for the observed clinical differences: STN-DBS may achieve its marked levodopa-sparing effect by directly modulating a key node in the indirect pathway, while GPi-DBS might more directly control dyskinesias by normalizing the abnormal output patterns that generate these involuntary movements.

Table 1. Comparative overview of STN-DBS and GPi-DBS in Parkinson's disease.

Aspect	STN-DBS	GPi-DBS
Primary Motor Benefits	Significant reduction in tremor, rigidity, bradykinesia; marked decrease in daily "off" time.	Comparable tremor control; strong direct antidyskinetic effect; potentially better for axial symptoms.
Levodopa Reduction	Often allows 30–50% reduction in dopaminergic medication.	Usually does not permit major medication reduction; controls dyskinesias directly.
Non-Motor Effects	May improve depression; risk of apathy, mild decline in verbal fluency/executive function; possible daytime sleepiness.	Generally neutral or slightly positive mood profile; minimal cognitive adverse effects.
Ideal Candidate Profile	Younger age, good levodopa response, tremor-dominant subtype, need for medication reduction.	Significant dyskinesias, axial symptoms, cognitive concerns, older patients.
Key Considerations	Requires careful neuropsychological screening; postoperative apathy management; battery life extended with adaptive systems.	Less medication flexibility; may be preferable in patients with mild cognitive impairment or psychiatric vulnerability.

Resting Tremor

Resting tremor, often the most recognizable sign of PD [6], is exquisitely responsive to DBS [15]. STN is considered the target of choice for comprehensive symptom control, including tremor [25-26]. STN-DBS produces rapid and dramatic tremor suppression, with 70-90% of patients experiencing significant relief immediately after surgery [17, 27]. This effect is remarkably durable, with studies reporting sustained benefit in 60-70% of patients after more than five years [20-21]. The mechanism is thought to involve the disruption of pathological oscillatory activity within the cerebello-thalamo-cortical circuit [28-30]. GPi-DBS also provides substantial tremor control, with reported efficacy rates of 60-80%, and some meta-analyses suggest comparable effects between STN and GPi for tremor suppression [23, 26]. For patients with severe, medication-refractory tremor as the dominant symptom, the ventral intermediate nucleus (Vim) of the thalamus can be used either alone or in combination with other targets (e.g., GPi plus Vim) to achieve superior tremor control, though it offers less benefit for other PD features like bradykinesia and rigidity [31-33].

Rigidity and Bradykinesia

Rigidity and bradykinesia are core symptoms that profoundly affect manual dexterity and movement initiation [34]. Both STN-DBS and GPi-DBS produce major improvements in these domains [15]. STN-DBS typically leads to a 40-60% reduction in limb rigidity scores on standardized scales like the UPDRS-III [22]. Bradykinesia, assessed through tasks like finger tapping, shows improvement with increased movement speed of 20-40% [17]. These effects are frequency-dependent, with stimulation above 130 Hz generally providing optimal results [35]. The underlying mechanism involves the modulation of the hyperdirect and indirect pathways, normalizing the excessive inhibitory output from the basal ganglia to thalamocortical projections [36-37]. GPi-DBS demonstrates broadly similar efficacy for rigidity and bradykinesia, though its mechanism is centered on direct modulation of the output nucleus of the basal ganglia [38]. The choice between targets for these symptoms is often influenced by other factors, such as the need for medication reduction or the presence of dyskinesias [15].

Postural Instability and Gait Disorders

Axial symptoms, including postural instability, freezing of gait (FOG), and festination, represent a major therapeutic challenge in advanced PD and are less predictably improved by DBS [39-40]. In the short to medium term (1-2 years), STN-DBS can provide meaningful benefit, reducing FOG episodes by 30-50% and improving gait speed [39-40]. However, its effect on postural reflexes is modest (20-30% improvement), and long-term studies indicate that the risk of falls often returns to baseline after five years, suggesting DBS does not halt the underlying neurodegenerative progression in brainstem locomotor centers [41]. GPi-DBS may offer a slight advantage over STN-DBS in maintaining postural stability, potentially due to differential effects on brainstem circuits [42-43]. To address this critical unmet need, novel targets are being explored. Low-frequency stimulation (60-80 Hz) of the STN or dedicated stimulation of the pedunculopontine nucleus (PPN), a key node in the mesencephalic locomotor region, has shown promise in further improving gait and balance, particularly FOG [44-45]. Innovative paradigms like variable-frequency stimulation, alternating between high and low frequencies, are under investigation to provide balanced improvement across all symptom domains [46-47].

Motor Complications

One of the most significant benefits of DBS is its ability to mitigate the long-term complications of levodopa therapy. DBS dramatically smooths out motor fluctuations. STN-DBS can reduce daily “off” time by approximately 50% and increase “on” time without troublesome dyskinesias by 3-4 hours per day [15, 48]. This is achieved through a combination of direct symptom control and the subsequent ability to significantly reduce dopaminergic medication (often by 30-50%) [49-50]. GPi-DBS also effectively increases “on” time, even without substantial medication reduction, by directly modulating the basal ganglia output [23].

Regarding levodopa-induced dyskinesias (LID), the two targets act through different mechanisms. GPi-DBS has a direct anti-dyskinetic effect, often reducing LID severity by over 50% shortly after activation, likely by suppressing the abnormal pallidal output driving dyskinetic movements [23]. STN-DBS primarily reduces LID indirectly by enabling major medication reduction, though some studies suggest a direct suppressive effect, especially when stimulating dorsal regions of the STN [51].

Combined Pharmacotherapy and DBS

While DBS markedly reduces motor fluctuations and levodopa-induced dyskinesias, it does not completely obviate the need for pharmacotherapy in most patients. Postoperative medication management is a nuanced process that must be individualized based on the stimulation target and the patient’s clinical response. For patients undergoing STN-DBS, the significant levodopa-sparing effect (typically 30-50% reduction) is a key advantage, allowing for substantial dose reduction of dopaminergic drugs to minimize side effects such as impulse control disorders and dopaminergic psychosis [49-50]. However, complete withdrawal is rarely advisable, as a baseline level of dopaminergic tone may be necessary to support non-motor functions and mood, and abrupt cessation can precipitate apathy or depression. In contrast, patients with GPi-DBS often require maintenance of their preoperative medication levels to achieve optimal motor benefit, as this target has less direct impact on medication requirements [23, 38].

Beyond dopaminergic drugs, the role of adjunctive medications remains important. For axial symptoms like freezing of gait that may persist or emerge despite optimal DBS and levodopa adjustment, agents such as MAO-B inhibitors (e.g., rasagiline) or amantadine can provide additional benefit [40, 47]. Furthermore, the management of non-motor symptoms, including depression, anxiety, and sleep disturbances, frequently necessitates the use of antidepressants, anxiolytics, or hypnotics in conjunction with DBS. The interaction between stimulation parameters and drug pharmacokinetics/pharmacodynamics is an area of ongoing investigation, with emerging evidence suggesting that closed-loop DBS systems may eventually enable real-time, automated coordination with medication cycles to further smooth out symptom fluctuations. Thus, DBS should be conceptualized not as a replacement for pharmacotherapy but as a powerful adjunct that, when optimally combined with medications, offers the best chance for comprehensive symp-

tom control in advanced PD.

Impact of DBS on Non-Motor Symptoms

The effects of DBS extend beyond the motor system, influencing neuropsychiatric, cognitive, and sleep domains. These non-motor outcomes are complex, variable, and critically important for overall patient well-being [52].

Neuropsychiatric Symptoms

DBS exerts nuanced effects on mood and behavior, heavily influenced by the stimulation target. STN-DBS can lead to improvements in depressive symptoms in many patients, potentially linked to the modulation of limbic circuits adjacent to the motor STN [53]. However, in 5-10% of cases, it can induce or exacerbate depression, possibly via interference with serotonergic projections [54]. GPi-DBS generally has a more neutral or slightly positive profile regarding mood [54]. Anxiety symptoms often improve with stimulation of either target, correlating with both direct neuromodulation and the secondary psychological benefit of improved motor function [53, 55]. A significant concern is the development of apathy, which can occur post-STN-DBS, potentially related to rapid dopamine agonist withdrawal or direct effects on motivational circuits [56]. Careful postoperative medication management and parameter adjustment are essential to mitigate these psychiatric risks [57].

Cognitive Function

The cognitive consequences of DBS are a critical consideration in patient selection and postoperative management [58]. STN-DBS is associated with mild but measurable declines in specific cognitive domains, particularly verbal fluency and executive functions (e.g., set-shifting, response inhibition), with meta-analyses confirming small-to-moderate effect sizes [54, 59]. These changes are more pronounced with bilateral stimulation and are thought to arise from multiple mechanisms.

A growing body of evidence implicates current spread from the motor territory of the STN to its adjacent associative and limbic subdivisions, which are involved in cognitive and emotional processing [60]. The STN is anatomically and functionally divided into three territories: the dorsolateral motor portion, the ventromedial associative portion, and the medial limbic portion. High-frequency stimulation optimized for motor symptom control may inadvertently modulate neurons or passing fibers within these non-motor territories, disrupting cognitive networks [60]. This is supported by diffusion tensor imaging studies showing that stimulation volumes intersecting with hyperdirect pathways from prefrontal cortex correlate with executive function declines.

Recent advances in resting-state functional MRI have provided deeper insights into the network-level effects of DBS. A pivotal study by Luo et al. demonstrated that cognitive decline following STN-DBS is associated with a widespread reduction in functional connectivity within cognitive-related brain networks, particularly the default mode network (DMN) and frontoparietal executive network [61]. Using preoperative and postoperative resting-state fMRI in patients with Parkinson's disease, the authors showed that individuals who exhibited significant cognitive deterioration at 12 months post-surgery had demonstrated greater stimulation-induced decreases in connectivity between the posterior cingulate cortex (a key DMN hub) and lateral prefrontal regions. Furthermore, the degree of connectivity reduction correlated with the magnitude of decline on neuropsychological tests of attention and executive function. This network-level mechanism suggests that DBS exerts its cognitive effects not merely through local modulation of the STN, but through broader disruption of large-scale brain networks that support cognitive processing.

Patient-specific factors significantly modulate this risk. Individuals with pre-existing mild cognitive impairment (MCI) are particularly vulnerable, likely due to reduced cognitive reserve and already-compromised network integrity [62-63]. Longitudinal studies indicate that while DBS itself does not increase the rate of conversion to dementia compared to the natural history of PD, patients with MCI at the time of surgery have a higher probability of progressing to dementia than non-operated patients with similar baseline cognitive status [62]. This underscores the necessity of rigorous preoperative neuropsychological screening to identify at-risk individuals.

In contrast, GPi-DBS appears to have a more favorable cognitive profile, with meta-analyses showing minimal negative impact and possible improvement in some executive tasks [52, 58]. This difference may reflect the anatomical position of the GPi as a downstream output nucleus, where stimulation effects are more confined to motor circuits with less spread to associative networks. Alternatively, the absence of a medication-sparing effect with GPi-DBS means that patients maintain their dopaminergic therapy, which may provide ongoing cognitive support, as dopamine is known to modulate prefrontal cortical function.

Sleep and Alertness

DBS can positively influence sleep architecture, primarily by alleviating nocturnal akinesia, pain, and tremor, thereby improving sleep continuity and increasing deep sleep (N3 stage) duration [64-65]. STN-DBS has been shown to reduce the severity of restless legs syndrome (RLS) in PD patients [66]. Its effect on REM sleep behavior disorder (RBD) is less clear, with studies reporting partial improvement in dream-enactment behaviors but persistence of abnormal muscle activity [67-68]. A notable side effect is the potential for STN-DBS to induce or exacerbate daytime sleepiness, possibly via inhibition of wake-promoting hypothalamic nuclei [69-70]. GPi-DBS's effects on specific sleep disorders like RLS and RBD are less studied but may follow a similar pattern of benefit driven by overall symptom improvement [64].

Prognostic Factors and Patient Selection

The success of DBS is not uniform; it is highly contingent on appropriate patient selection. Identifying robust predictors of outcome is paramount for maximizing benefit and minimizing risk [71-72].

Levodopa Responsiveness

A positive response to a preoperative levodopa challenge test is the strongest independent predictor of favorable motor outcome after DBS [71-72]. An improvement of ≥30% in the UPDRS-III motor score during the "on" medication state is widely used as a key inclusion criterion [15, 16, 22]. This response indicates the presence of a functional dopaminergic system and

suggests that the patient's disability is primarily due to dopaminergic deficiency rather than unresponsive non-dopaminergic pathology (e.g., widespread Lewy body disease affecting cholinergic or noradrenergic systems) [72]. While predictive of excellent short- and medium-term outcomes, the predictive value of the levodopa test may diminish for very long-term prognosis (>5 years) as non-dopaminergic symptoms emerge [73].

Disease Duration and Age at Surgery

Shorter disease duration is consistently associated with superior and more durable motor outcomes after DBS [71]. Patients with advanced disease and long duration (>10 years) often have significant involvement of non-dopaminergic systems (e.g., pedunculopontine nucleus, locus coeruleus), leading to axial symptoms, cognitive impairment, and autonomic dysfunction that are less amenable to DBS [74-75]. Consequently, there is a growing trend toward considering DBS at an earlier stage, once troublesome motor complications emerge, to preserve quality of life and possibly achieve better long-term functional outcomes [76].

Younger age at surgery is another favorable prognostic factor, linked to greater neural plasticity, better tolerance of stimulation, a lower burden of comorbidities, and a longer horizon to benefit from the therapy [75-76]. Older patients (>70-75 years) may have reduced surgical and cognitive reserve, higher rates of brain atrophy (increasing surgical risk), and more vascular comorbidities (e.g., leukoaraiosis), which can limit DBS efficacy and increase perioperative complication rates [77-78].

Motor Phenotype

The predominant preoperative motor phenotype influences DBS outcome [72]. The "tremor-dominant" subtype is associated with excellent and sustained response to both STN and GPi DBS [79]. In contrast, patients with the "postural instability/gait difficulty" (PIGD) phenotype typically experience less robust and less durable improvement, particularly for their axial symptoms [80]. This subtype is also linked to faster disease progression and higher prevalence of cognitive decline [81]. These differences suggest underlying variations in the topographic spread of pathology and neurochemical deficits among PD subtypes [80-81].

An emerging conceptual framework with potential relevance to DBS outcomes is the classification of PD into "brain-first" and "body-first" subtypes based on the initial site of α-synuclein pathology accumulation. Although direct evidence examining DBS outcomes stratified by these subtypes is currently limited, theoretical considerations suggest possible differences in treatment response. Patients with the body-first subtype, characterized by earlier and more RBD and greater brainstem pathology [68], may be predisposed to persistent axial symptoms post-DBS due to greater involvement of non-dopaminergic brainstem locomotor centers such as the pedunculopontine nucleus [39, 44]. Conversely, brain-first patients, who have a higher propensity for cognitive decline and neuropsychiatric features, may face increased risks of postoperative cognitive deterioration if stimulation spreads to non-motor territories [61-62]. This framework highlights the importance of assessing non-motor features, particularly RBD and cognitive status, when counseling patients about expected outcomes, and prospective studies incorporating these variables are needed to formally test whether this classification can refine patient selection.

Cognitive and Psychiatric Baseline

Preoperative cognitive status is a critical determinant of postoperative outcome and risk [59]. Significant cognitive impairment or dementia is a contraindication to DBS, as surgery can worsen cognition and does not improve functional independence in this population [52]. The presence of MCI necessitates careful counseling, as it increases the risk of further decline [59, 63]. Similarly, active, untreated major depression, anxiety, or psychosis are contraindications, as DBS can exacerbate these conditions [15, 16, 22]. Stable, well-managed psychiatric disorders require close multidisciplinary management perioperatively [52, 58].

Technological Developments and Future Directions

The field of DBS is rapidly evolving beyond traditional, constant-parameter ("open-loop") stimulation [82-83].

Adaptive or Closed-Loop DBS (aDBS)

aDBS represents a paradigm shift. Instead of delivering fixed stimulation, aDBS systems use implanted sensors to record local field potential (LFP) [84-85], such as beta-band oscillations from the STN, which correlate with motor symptom severity [86]. The stimulator then automatically adjusts its output in real-time based on this neural feedback [87]. Early clinical studies show that aDBS can provide equivalent or superior symptom control compared to conventional DBS while significantly reducing total stimulation energy delivery, potentially extending battery life and reducing stimulation-induced side effects [88-89].

Directional Steering and Current Fractionation

Modern DBS leads with multiple segmented contacts allow for "directional" steering of the electrical field [90]. This enables clinicians to shape the volume of tissue activated, more precisely targeting the therapeutic zone while avoiding stimulation of adjacent structures responsible for side effects (e.g., corticospinal tract causing muscle contractions, medial limbic STN affecting mood) [91]. This technology enhances the therapeutic window and allows for more personalized programming [92].

Novel Targets and Multi-Target Stimulation

To address therapy-resistant symptoms, new targets are being investigated. As mentioned, PPN stimulation for gait and balance is a primary focus [44, 93]. The substantia nigra pars reticulata (SNr) and the zona incerta are also being explored [31]. Furthermore, the simultaneous use of two targets (e.g., STN plus PPN, GPi plus Vim) in a single patient via a single or dual generator system is being studied to provide a broader spectrum of symptom control [32].

Future Research and Critical Perspectives

Despite its established efficacy, several critical questions remain. Long-term (>10 year) outcomes data, especially regarding the evolution of non-motor symptoms and quality of life,

are still maturing [21]. The optimal timing of DBS intervention is an area of active debate and ongoing clinical trials (e.g., the EARLYSTIM study extension) in balancing early benefits against surgical risks and natural disease progression [71, 76]. Further refinement of patient selection biomarkers, beyond clinical assessments, using neuroimaging, genetics, and electrophysiology, is needed [72]. Finally, the cost-effectiveness and accessibility of DBS, along with the development of even less invasive neuromodulation techniques, will be crucial for broadening its global impact [14].

Conclusion

Deep Brain Stimulation has irrevocably changed the treatment landscape for advanced PD. It is a highly effective therapy for ameliorating levodopa-responsive motor symptoms and reducing debilitating motor complications, with proven long-term benefits. The choice between STN and GPi involves a nuanced trade-off, considering desired medication reduction, the profile of motor symptoms (especially axial features), and the patient's cognitive and psychiatric status. The non-motor effects of DBS are multifaceted and necessitate comprehensive preoperative assessment and postoperative management. The robustness of the outcome is heavily dependent on careful patient selection, with preoperative levodopa responsiveness, disease duration, phenotype, and cognitive/psychiatric health serving as key prognosticators.

The future of DBS lies in personalization and technological sophistication. Adaptive closed-loop systems, directional leads, and exploration of novel targets promise to enhance efficacy, reduce side effects, and tackle currently unmet needs like gait freezing. As research continues to refine patient selection criteria and stimulation strategies, DBS will solidify its role not merely as a last-resort intervention, but as an integral component of a personalized, staged therapeutic strategy for PD, aimed at preserving function and quality of life throughout the course of the disease.

Abbreviations

PD, Parkinson's disease; DBS, deep brain stimulation; GPi, globus pallidus internus; STN, subthalamic nucleus; LID, levodopa-induced dyskinesias; SNr, substantia nigra pars reticulata; GPe, globus pallidus externus; FOG, freezing of gait.

Acknowledgements

None.

Author Contributions

SW designed the study, collected data, analyzed data, illustrated figures, drafted the manuscript, and revised the manuscript. XL, RW, and RM collected data, analyzed data, and revised the manuscript. AY and FM designed the study, collected data, analyzed data, and revised the manuscript. JZ is the team leader who designed the study, collected data, analyzed data, and revised the manuscript. All authors have read and approved the final manuscript.

Funding Information

None.

Ethics Approval and Consent to Participate

N/A.

Competing Interests

The authors declare that they have no conflict of interest.

Data Availability

The data that support the findings of this study are included in the article/supplementary material.

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Review Article Brain Conflux

Neuromodulation and Electrophysiological Monitoring in Headache Management: Current Advances and Future Perspectives

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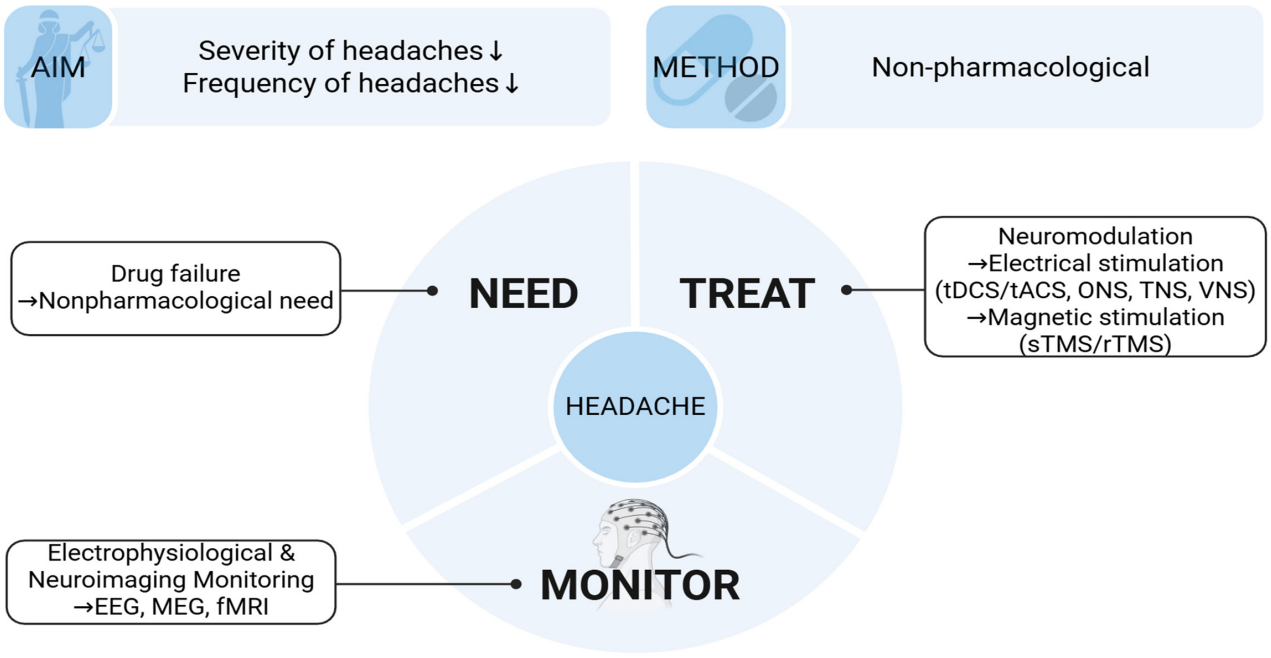
Graphical Abstract



https://doi.org/10.71321/vah93v44

Review Article

Brain Conflux

Neuromodulation and Electrophysiological Monitoring in Headache Management: Current Advances and Future Perspectives

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Received: 2025-09-26 | Accepted: 2025-12-02 | Published online: 2026-04-12

Abstract

Headache disorders such as migraine are major causes of disability worldwide. Pharmacological treatments are often insufficient, particularly in resistant or refractory cases. Neuromodulation techniques, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and peripheral approaches such as occipital nerve stimulation (ONS), trigeminal nerve stimulation (TNS), sphenopalatine ganglion (SPG) stimulation, and non-invasive vagus nerve stimulation (nVNS), offer promising alternatives. Electrophysiological methods including electroencephalography (EEG), magnetoencephalography (MEG), evoked potentials, and TMS combined with EEG (TMS-EEG) provide mechanistic insights and potential biomarkers for treatment monitoring and personalization. Here, we summarize emerging findings on neuromodulation and electrophysiological biomarkers in headache disorders, highlight their mechanistic underpinnings, and propose future directions for optimizing individualized treatment strategies. Key challenges remain, including small sample sizes, heterogeneous stimulation protocols, and limited long-term data. Future research should prioritize multicenter randomized controlled trial (RCT), closed-loop neuromodulation, and multimodal integration to advance precision headache medicine.

Keywords: headache; neuromodulation; electrophysiological monitoring; neuroimaging

Introduction

Headache disorders, particularly migraine and cluster headache, represent a leading cause of neurological disability worldwide, exerting profound impacts on patients' quality of life, workforce productivity, and healthcare systems [1]. Although pharmacological treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), triptans, and calcitonin gene-related peptide (CGRP) antagonists remain the mainstay of therapy, their effectiveness is often limited, and many patients struggle with inadequate response, side effects, or medication overuse [2].

A particularly challenging subgroup is composed of patients with resistant or refractory migraine, defined by inadequate response to at least three preventive drug classes (resistant) or to all available classes (refractory) [3]. These patients, often burdened by ≥8 monthly days of disabling headaches, are thought to suffer from complex pathophysiological mechanisms involving maladaptive synaptic plasticity, central sensitization, and altered hypothalamic–limbic connectivity [3]. For them, conventional pharmacological strategies are frequently unsatisfactory, creating an urgent need for effective non-pharmacological approaches.

Neuromodulation has emerged as a promising strategy in this context (Figure 1). By applying electrical or magnetic stimulation, neuromodulation techniques aim to regulate abnormal excitability and dysfunctional network activity in both central and peripheral nervous systems. Several non-invasive devices have already received Food and Drug Administration (FDA) approval for headache management, including single-pulse transcranial magnetic stimulation (sTMS), non-invasive vagus nerve stimulation (nVNS), and transcutaneous supraorbital stimulation (tSNS) [4]. Furthermore, electrophysiology not only provides mechanistic validation but also holds promise for developing biomarkers to monitor treatment response and guide individualized neuromodulation strategies [5-7]. The specific mechanisms of action and primary central or peripheral targets for these neuromodulation techniques are summarized in Table 1.

Transcranial magnetic stimulation

TMS is a non-invasive neuromodulation technique that induces cortical currents via magnetic fields [8]. TMS and repetitive

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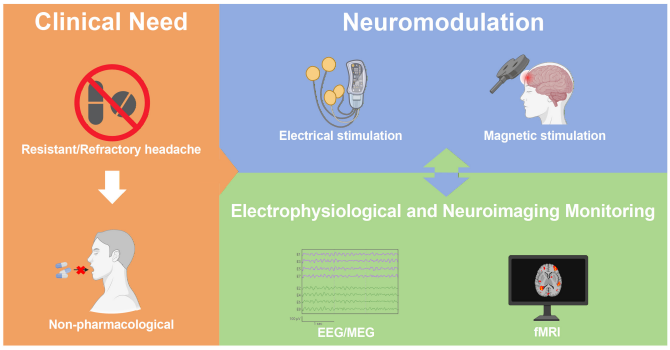
Figure 1. Conceptual framework of neuromodulation and electrophysiological monitoring in headache management.
Clinical need arises from resistant and refractory headache, where conventional pharmacological strategies often fail. Neuromodulation approaches, including electrical stimulation (e.g., transcranial direct current stimulation, vagus nerve stimulation, occipital nerve stimulation) and magnetic stimulation (e.g., single-pulse or repetitive transcranial magnetic stimulation), provide non-pharmacological treatment alternatives. Electrophysiological monitoring techniques, such as electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI), offer mechanistic insights and potential biomarkers to guide personalized interventions and facilitate closed-loop neuromodulation strategies.



firmed that sTMS provides significant acute relief in migraine attacks and prolongs pain-free intervals in a subset of patients [12].

rTMS has been more extensively studied as a preventive therapy. High-frequency stimulation (5–10 Hz) enhances cortical excitability, while low-frequency stimulation (1 Hz) reduces hyperexcitability. rTMS targeting the primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) has shown benefits in reducing headache frequency and severity in chronic migraine [13-14]. Additionally, rTMS has been explored in cluster headache, particularly in refractory cases, with promising though preliminary results [15].

TMS-electroencephalography (EEG) studies have revealed disrupted excitatory–inhibitory balance in migraineurs. Resting motor thresholds (RMT) and phosphene thresholds (PT) are often fluctuating, with migraine with aura patients typically showing increased cortical excitability [16-18]. Importantly, rTMS has been shown to normalize habituation deficits in visual and somatosensory evoked potentials, suggesting that it acts by modulating impaired synaptic plasticity [19].

At the network level, TMS likely exerts therapeutic effects through reshaping abnormal thalamo-cortical excitability [20]. This aligns with EEG/magnetoencephalography (MEG) findings of increased low-frequency (δ, θ) and reduced α oscillations in migraine, supporting the hypothesis that neuromodulation restores pathological oscillatory dynamics.

Electrical neuromodulation

Transcranial direct current stimulation (tDCS) applies weak direct currents (typically 1–2 mA) between scalp electrodes to modulate neuronal resting membrane potentials, thereby altering cortical excitability. Anodal stimulation induces depolarization and increases excitability, whereas cathodal stimulation induces hyperpolarization and decreases excitability. In migraine, tDCS has been applied to the DLPFC, M1, and occipital visual cortex [21]. Clinical trials have reported that anodal tDCS over the DLPFC alleviates pain sensitization [22], while cathodal tDCS over the occipital cortex may reduce visual aura and lower photic sensitivity thresholds [23]. Several randomized controlled trial (RCT) have shown reductions in attack frequency and medication use, supporting the preventive role of tDCS in chronic migraine [24]. Transcranial alternating current stimulation (tACS) delivers sinusoidal currents at specific frequencies, entraining endogenous brain oscillations and modulating frequency-specific activity. Although still in early stages of investigation, tACS shows preliminary efficacy in headache research. Preliminary findings suggest that tACS over the visual cortex has the potential to terminate migraine attacks [25].

Deep brain stimulation (DBS) represents an important, though highly specialized, neuromodulation option for patients with medication-refractory cluster headache. A growing body of case reports and small case series has demonstrated that stimulation of deep pain-modulating structures—most notably the posterior hypothalamus and, more recently, the ventral tegmental area—can achieve meaningful and sustained reductions in attack frequency and pain severity in a majority of treated patients. These findings highlight the pivotal role of hypothalamic–brainstem circuits in cluster headache pathophysiology. Although sample sizes remain limited and the

Table 1. Neuromodulation techniques in headache management.

Neuromodulation method	Mechanism of action	Primary targets
sTMS/rTMS	Modulates cortical excitability; suppresses CSD; reshapes thalamo-cortical network activity	Visual cortex, M1, DLPFC
tDCS	Alters resting membrane potentials; anodal increases excitability, cathodal decreases excitability	DLPFC, M1, occipital cortex
tACS	Entrainment of brain oscillations; phase alignment with endogenous rhythms	Visual cortex, thalamo-cortical circuits
ONS	Modulates nociceptive transmission in trigeminovascular system	Greater occipital nerve
TNS/t-SNS	Alters trigeminal nociceptive pathways; modulates brainstem excitability	Supraorbital and supratrochlear branches of trigeminal nerve
SPG stimulation	Modulates parasympathetic outflow and craniofacial autonomic reflexes	Sphenopalatine ganglion
VNS/nVNS	Influences parasympathetic pathways and brainstem networks; modulates pain and autonomic regulation	Vagus nerve

procedure carries inherent neurosurgical risks, DBS offers a potential therapeutic avenue for the small subset of individuals who fail to benefit from all available pharmacological and peripheral neuromodulation strategies. Ongoing refinements in targeting, imaging guidance, and device programming are expected to further optimize safety and long-term efficacy [26].
Electrophysiological monitoring (EEG, MEG, evoked potentials) provides insights into the mechanisms of tDCS/tACS. Studies indicate that tDCS can normalize habituation deficits in visual and somatosensory evoked potentials, pointing to its role in restoring aberrant synaptic plasticity [27]. Meanwhile, tACS achieves phase alignment with endogenous oscillations, modulating thalamo-cortical dynamics and laying the groundwork for closed-loop neuromodulation paradigms [28].
Despite promising evidence, current applications of tDCS/tACS are limited by heterogeneity in electrode placement, stimulation parameters, and outcome measures, resulting in inconsistent reproducibility. Small sample sizes and short follow-up periods further restrict guideline-level recommendations. Future research should focus on large-scale, multicenter RCT and on integrating electrophysiological biomarkers to optimize individualized stimulation protocols.

Peripheral stimulation

Occipital nerve stimulation (ONS) is one of the most extensively studied neuromodulation approaches. Initially designed for occipital neuralgia, ONS has since been investigated in chronic migraine and cluster headache. Multiple RCT demonstrated that ONS significantly reduces headache days and improves disability scores such as Migraine Disability Assessment (MIDAS) in chronic migraine [29-32].
External trigeminal/supraorbital nerve stimulation (t-SNS), exemplified by the Cefaly® device, has gained FDA approval for migraine prophylaxis. The trigeminal nerve carries sensory components for much of the head and innervates muscles in the lower jaw. It then divides into the ophthalmic (V1), maxillary (V2), and mandibular (V3) branches. The PREMICE multicenter RCT showed that t-SNS reduces migraine frequency with minimal adverse effects, mostly limited to transient paresthesia [33]. Compared with oral preventives, t-SNS offers a superior safety profile, making it suitable for patients intolerant or unwilling to use daily medications. The first RCT to show the effectiveness of non-invasive supraorbital and supratrochlear peripheral nerve stimulation (PNS) for migraines was completed by Schoenen et al. in 2013. In this study, 67 patients with at least two migraine attacks per month were randomized to either sham or stimulation with daily sessions of tSNS with Cefaly device. After 3 months of treatment, the stimulation group experienced a significant reduction in the average number of migraine days, with 38% achieving a >50% response. This study overall demonstrated a 26% therapeutic gain, which is within the range of those reported for other commonly used migraine treatments [34].
The sphenopalatine ganglion (SPG) plays a pivotal role in craniofacial autonomic pathways and cluster headache pathophysiology. Implantable SPG microstimulators, activated by patients during attacks, have demonstrated efficacy in aborting acute cluster headache episodes and in reducing attack frequency in long-term follow-up [35].
Both invasive and nVNS have been studied. Non-invasive VNS (nVNS, e.g., GammaCore®) has been FDA approved for cluster headache and migraine. RCTs confirmed its effectiveness in acute cluster headache treatment and in reducing headache frequency in some chronic migraine patients [36-39]. The PREVA trial demonstrated that adjunctive nVNS significantly reduced chronic cluster headache attacks (−5.9 vs. −2.1 per month) and achieved ≥50% pain reduction in 40% of patients versus 8.3% in controls [40]. In ACT1, nVNS was effective for acute episodic cluster headache but not chronic cases, with Goadsby et al. reporting similar European findings [37-38]. For migraine, the EVENT study found no significant preventive effect at 2 months, but extended open-label use showed reduced headache days [36]. The PRESTO trial confirmed that nVNS significantly improved acute migraine pain freedom between 30–120 minutes, provides clinically meaningful pain relief in selected endpoints comparable to pharmacologic treatments [39]. Overall, nVNS appears more effective in episodic cluster headache and acute migraine, while its preventive role in chronic migraine requires further validation.
ONS, trigeminal nerve stimulation (TNS), SPG, and VNS represent promising neuromodulatory strategies, particularly for resistant and refractory migraine patients (≥3 preventive drug failures). However, challenges remain, including heterogeneity in devices and stimulation parameters, limited sample sizes and follow-up duration, and barriers related to cost and accessibility. Future directions should emphasize large-scale RCTs, integration with electrophysiological biomarkers, and development of personalized stimulation protocols. A comprehensive overview of typical parameters, clinical outcomes, adverse events, and current evidence levels for these neuromodulation modalities is provided in Table 2.

Electrophysiological and neuroimaging monitoring in headache treatment

Headache—especially migraine—is marked by cyclical dysfunction of thalamo-cortical circuits and sensory processing [41]. Converging evidence from EEG/MEG/functional magnetic resonance imaging (fMRI) supports abnormal thalamo-cortical coupling and enhanced low-frequency oscillations even interictally, providing quantifiable targets and response markers for neuromodulation. According to Puledda et al., interictal migraineurs typically display reduced alpha and enhanced slow rhythms (theta/delta), predominantly in posterior regions, which tend to normalize as the attack approaches. Visual and somatosensory evoked potentials consistently demonstrate a deficit of habituation, with responses potentiating rather than decrementing across blocks; this abnormality often reverses during the ictal phase, pointing to dysfunction of synaptic plasticity mechanisms [19]. Gomez-Pilar et al. systematically reviewed 24 studies (EEG/MEG/fMRI) and highlighted medium-to-fast frequency bands, especially the beta band, as promising biomarkers to differentiate chronic migraine (CM) from episodic migraine (EM). EEG and MEG findings showed significantly higher high-beta power in CM, while MEG connectivity analyses revealed reduced beta-band node strength in anterior cingulate, insula, and somatosensory cortices in CM patients, linking beta-band dysfunction to migraine chronification [42].
TMS-EEG uncovers abnormal excitatory/inhibitory recruitment in migraine, particularly with aura. Findings include paradoxical responses to inhibitory rTMS/tDCS protocols, reflecting malfunctioning of short-term depression/long-term depression plasticity mechanisms [43]. Techniques like paired associative

stimulation (PAS) and short-latency afferent inhibition (SAI) confirm disrupted thalamo-cortical GABAergic and cholinergic control, which fluctuates across migraine phases, reinforcing the theory of migraine as a disorder of abnormal synaptic plasticity [44-46].

Differences between CM and EM are consistent across modalities (EEG, MEG, fMRI, PET), supporting electrophysiological monitoring as a candidate tool for biomarker-based subtyping, prognosis, and individualized treatment strategies. For instance, EEG/MEG studies reveal higher relative beta power and altered connectivity strength in CM compared to EM, while fMRI and PET findings point to disrupted pain-processing networks and metabolic abnormalities in the anterior cingulate, insula, and thalamus. This multimodal convergence underscores the robustness of electrophysiological alterations as state markers of migraine progression [42]. From a clinical standpoint, such biomarkers could aid in distinguishing patients at risk of chronification, guiding early escalation to preventive or neuromodulatory therapies. Machine-learning models integrating electrophysiological, neuroimaging, and clinical features have shown promise in predicting which patients are most likely to benefit from specific neuromodulation interventions. Such data-driven approaches may enable individualized treatment selection by identifying neural signatures associated with favorable therapeutic response. In addition, electrophysiological metrics—such as habituation deficits, beta-band oscillatory changes, and thalamo-cortical dysrhythmia—may complement clinical scales (e.g., MIDAS, HIT-6) to refine disease burden assessment and stratify patients for targeted interventions. These tools could also improve the identification of subgroups likely to benefit from specific neuromodulation approaches (e.g., TMS for cortical hyperexcitability, tACS for oscillatory entrainment). Importantly, electrophysiological monitoring may bridge the gap between phenotype and treatment personalization: CM and EM patients differ not only in headache frequency but also in their neurophysiological signatures, which may explain variability in therapeutic response. By integrating electrophysiological biomarkers into clinical trials and real-world monitoring, clinicians could move toward precision headache medicine, tailoring preventive strategies and neuromodulation parameters according to an individual's cortical and network-level profile.

Other neuromodulation approaches such as ultrasound neuromodulation and photobiomodulation have also been explored for headache treatment; however, evidence remains scarce. More robust clinical trials are needed to determine their therapeutic value.

Conclusion

Clinically, a considerable subset of patients—particularly those with resistant or refractory migraine—remain poorly responsive to conventional pharmacological strategies [3], highlighting an urgent need for neuromodulation as an alternative or adjunctive treatment. Closed-loop neuromodulation represents an emerging strategy in which stimulation parameters are continuously adapted based on real-time neural signals, allowing more precise engagement of pathophysiological circuits implicated in migraine. Compared with traditional open-loop paradigms, closed-loop systems have the potential to enhance therapeutic efficacy, reduce unnecessary stimulation, and minimize adverse effects. Integrating multimodal neuroimaging (e.g., fMRI, structural MRI, DTI) with electrophysiological measures (EEG/MEG) can further refine individualized therapy by identifying patient-specific biomarkers, mapping dysfunctional networks, and guiding stimulation timing and location. Such multimodal approaches could ultimately enable personalized, adaptive neuromodulation, improving long-term outcomes in patients with refractory or resistant migraine. At the same time, electrophysiological monitoring (EEG, MEG, evoked potentials, TMS-EEG) has provided unique insights into dynamic network alterations and abnormal synaptic plasticity mechanisms across the migraine cycle [19], while also emerging as a candidate biomarker for clinical subtyping and prognosis (chronic vs. episodic migraine) [41].

Challenges and Future Directions

Despite promising advances, the clinical application of neuromodulation and electrophysiological monitoring in headache medicine still faces significant challenges. First, limited trial design and small sample sizes remain a major barrier. Most

Table 2. Summary of neuromodulation modalities for migraine.

Modality	Typical Parameters	Treatment Duration	Primary Outcomes	Adverse Events	Evidence Level
TMS (s/rTMS)	1–10 Hz or single-pulse; intensity 80–120% RMT	Acute: single session; Preventive: 10–20 sessions over 2–4 weeks	Reduction in headache days, acute pain relief	Scalp discomfort, transient dizziness	Moderate
tDCS/tACS	tDCS: 1–2 mA; tACS: 10–40 Hz	20–30 min/day, 5–10 days or repeated cycles	Reduced headache frequency; modulation of cortical excitability	Mild tingling, erythema	Low–moderate
ONS	Implantable pulse generator; 60–90 Hz	Long-term chronic stimulation	Reduction in headache days in chronic migraine	Lead migration, infection, local pain	Moderate
TNS	60–120 Hz, 250 μs pulse width	Daily 20–60 min sessions	Reduced monthly migraine days; acute relief	Local paresthesia, skin irritation	High for prevention
SPG Stimulation	Implantable microstimulator	Acute, on-demand stimulation	Pain relief during attacks, reduced autonomic symptoms	Facial numbness, device discomfort	Moderate
VNS/nVNS	1–5 kHz burst stimulation	Acute: 2–3 cycles per attack; Preventive: multiple cycles/day	Reduced attack frequency and pain intensity	Hoarseness, neck tingling	Moderate

studies are single-center with short follow-up, contributing to heterogeneity in reported outcomes. For instance, RCTs of ONS in chronic migraine have yielded conflicting results, with some showing significant reductions in headache days, while others failed to demonstrate superiority over sham [47]. Similarly, in the EVENT trial of nVNS for migraine prevention, no short-term benefit was observed, with improvements only emerging in a longer open-label phase [35]. Second, heterogeneity in stimulation parameters and techniques hinders reproducibility. Studies vary considerably in target site, stimulation intensity, frequency, and treatment duration, especially for tDCS/tACS, where electrode placement and dosing paradigms differ widely. Device-specific variability and operator expertise further complicate cross-study comparisons. Third, unclear linkage between mechanisms and clinical efficacy poses another challenge. Although EEG/MEG and TMS-EEG studies consistently demonstrate abnormal synaptic plasticity and thalamo-cortical dysrhythmia in migraine, it remains uncertain whether these markers directly mediate therapeutic response, limiting their reliability as predictive biomarkers. However, neuromodulation remains a rapidly evolving field with significant potential to transform headache management.

Abbreviations

TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; tACS, ranscranial alternating current stimulation; ONS, occipital nerve stimulation; TNS, trigeminal nerve stimulation; SPG, sphenopalatine ganglion; nVNS, non-invasive vagus nerve stimulation; EEG, electroencephalography; MEG, magnetoencephalography; RCT, randomized controlled trial; NSAIDs, non-steroidal anti-inflammatory drugs; CGRP, calcitonin gene-related peptide; FDA, Food and Drug Administration; sTMS, single-pulse transcranial magnetic stimulation; nVNS, non-invasive vagus nerve stimulation; tSNS, transcutaneous supraorbital stimulation; rTMS, repetitive TMS; CSD, cortical spreading depression; DLPFC, dorsolateral prefrontal cortex; RMT, resting motor thresholds; PT, phosphene thresholds; DBS, deep brain stimulation; MIDAS, Migraine Disability Assessment ; PNS, peripheral nerve stimulation; fMRI, functional magnetic resonance imaging; CM, chronic migraine; EM, episodic migraine; PAS, paired associative stimulation; SAI, short-latency afferent inhibition.

Acknowledgements

We acknowledge that parts of the graphical materials were prepared using external design platforms (BioRender). The copyrights for these templates and design elements belong to their respective owners.

Author Contributions

DQ and WW conceptualized the review and supervised the project. QD, XL, WTL conducted the literature review and drafted the manuscript.

Funding Information

Not applicable.

Ethics Approval and Consent to Participate

Not applicable.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

Not Applicable.

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[1] Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. (2024). Lancet, 403(10440), 2133-2161. https://doi.org/10.1016/s0140-6736(24)00757-8

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Case Report Brain Conflux

Interception of Lipid-rich Emboli Using an Embolic Protection Device during Carotid Artery Stenting: A Case Report

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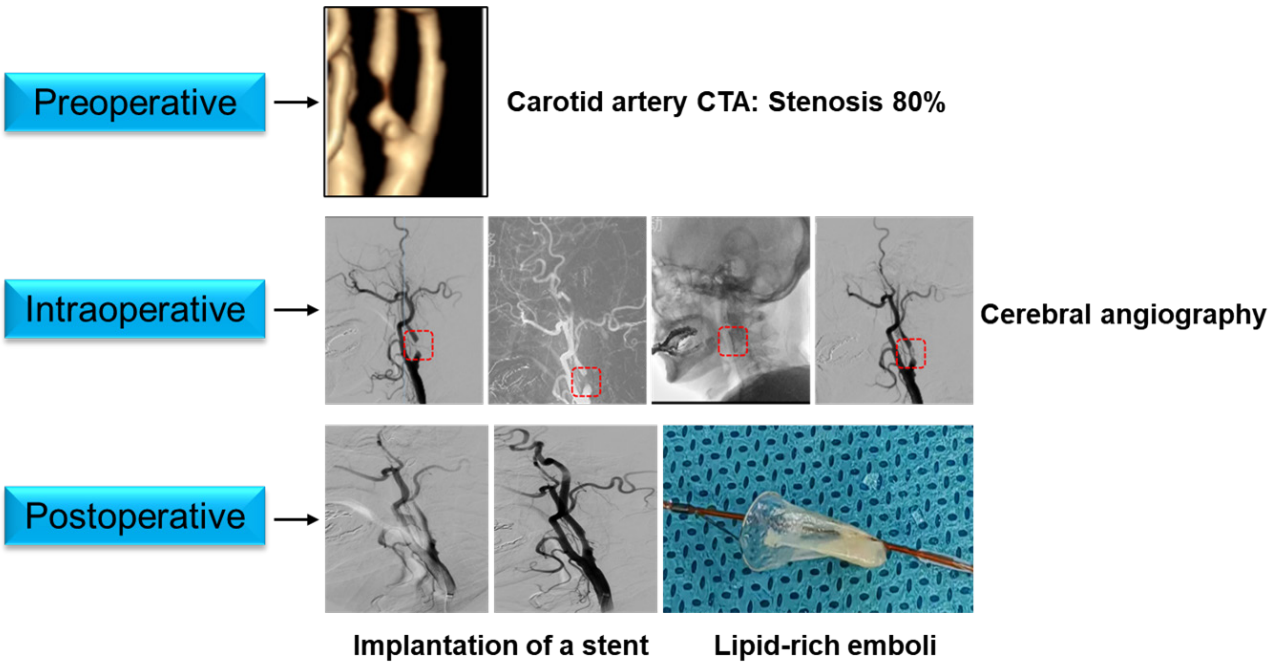
Graphical Abstract



https://doi.org/10.71321/94w1v584

Case Report

Brain Conflux

Interception of Lipid-rich Emboli Using an Embolic Protection Device during Carotid Artery Stenting: A Case Report

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Received: 2025-09-25 | Accepted: 2025-12-01 | Published online: 2026-04-12

Abstract

Carotid artery stenosis is a major risk factor for ischemic stroke, and carotid artery stenting (CAS) has become a crucial minimally invasive treatment, especially for patients with poor surgical tolerance. This case report focuses on a 73-year-old male patient with severe right internal carotid artery stenosis (80%), complicated by hypertension, a history of cerebral infarction, and recurrent transient ischemic attack (TIA). Preoperative dual anti-platelet therapy was administered, and CAS was performed using a distal filter-type embolic protection device (EPD) to intercept lipid-rich embolism. Importantly, transient bradycardia and hypotension occurred due to carotid sinus reflex but were successfully managed with atropine and dopamine. Postoperative digital subtraction angiography (DSA) showed that the residual stenosis rate was reduced from 80% to <10%, with unobstructed blood flow. During 1-month follow-up, the patient's symptoms resolved, and carotid ultrasound confirmed no in-stent re-stenosis. This case demonstrates that CAS with EPD is safe and effective for severe carotid artery stenosis, as the EPD can significantly reduce the risk of cerebral embolism by intercepting dislodged emboli. The findings provide valuable clinical experience for improving treatment outcomes and patient prognosis in similar cases.

Keywords: Carotid Artery Stenting; Embolic Protection Device; Severe Carotid Artery Stenosis; Transient Ischemic Attack

Introduction

Carotid artery stenosis holds an extremely important position in cerebrovascular diseases and is one of the key risk factors for ischemic stroke. With the intensification of population aging and changes in lifestyle, the incidence of carotid artery stenosis has been increasing year by year, seriously threatening human health and quality of life. According to relevant statistical data, ischemic stroke accounts for more than 4/5 of all cerebrovascular diseases worldwide [1]. In China, due to unhealthy factors such as high-salt and high-fat diets of the public, the incidence of basic diseases such as hypertension, diabetes, and hyperlipidemia is relatively high, which leads to a much higher incidence of carotid artery stenosis than the global average, about 5% to 7% [2].

As the main blood vessel that supplies oxygen-rich blood to the brain, once carotid artery stenosis occurs, it will lead to insufficient blood supply to the brain, causing a series of serious clinical symptoms. Patients with mild to moderate carotid artery stenosis may experience symptoms such as dizziness and limb weakness due to insufficient blood supply to the brain; while patients with severe carotid artery stenosis, due to severe vascular blockage, have a more serious situation of cerebral ischemia, with a risk of cerebral ischemia as high as 26% within two years, and are extremely prone to cerebral infarction, leading to hemiplegia, aphasia, hemisensory disturbance and other severe neurological deficits, and even life-threatening [3]. In addition, unstable plaques at the carotid artery may also detach and enter the brain with the blood flow, causing multiple cerebral infarctions and repeated attacks, causing severe pain in patients and seriously affecting their self-care ability and social function.

Carotid artery stenosis is mainly caused by atherosclerosis. When the vessel wall is gradually eroded by fat, cholesterol and other substances, forming plaques, the vessel diameter narrows, hindering blood flow. This pathological process is often insidious, and many patients are unaware of the disease progression until severe clinical symptoms occur, at which point the condition may be quite serious, making treatment more difficult and the prognosis relatively poor.

Currently, the main treatment methods for carotid artery ste-

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nosis include drug therapy, carotid endarterectomy (CEA), and carotid artery stenting (CAS) [4-5]. Drug therapy is mainly used for patients with mild carotid artery stenosis or as an adjunct to surgical treatment, by controlling blood pressure, blood sugar, and blood lipids, and using antiplatelet drugs and statins, etc., to delay the progression of the disease. However, for patients with moderate to severe carotid artery stenosis, the effect of drug therapy alone is limited. CEA is a traditional surgical method that removes atherosclerotic plaques in the carotid artery to restore vascular patency, effectively reducing the risk of stroke in patients with carotid artery stenosis, and is widely used in Europe and America. However, CEA has a relatively large surgical trauma, high requirements for the patient's physical condition, and relatively high surgical risks, and there are certain postoperative complications, such as cranial nerve palsy, wound infection, and cervical hematoma, etc.

With the advancement of medical technology and the development of medical materials, CAS, as a minimally invasive, safe and effective method, has become an important means of treating carotid artery stenosis, especially suitable for patients with poor physical conditions who cannot tolerate CEA or have contraindications to surgery [6]. It restores cerebral blood supply by implanting a stent to expand the narrowed vessel, and an embolic protection device (EPD) is placed at the distal end of the stenosis during the operation to intercept detached emboli, reducing the risk of cerebral embolism and enhancing the safety of the operation.

Materials and Methods

Patient Information

A 73-year-old male patient with:

Chief complaint: Numbness and weakness in the left hand, progressive worsening over 3 days.

Comorbidities: 15-year history of hypertension (max blood pressure: 200/130 mmHg, managed with sacubitril/valsartan and amlodipine besylate), 2-year history of cerebral infarction (residual slurred speech), dyslipidemia (total cholesterol: 6.8 mmol/L, triglycerides: 2.5 mmol/L, low-density lipoprotein cholesterol: 4.5 mmol/L), and poor glycemic control (glycated hemoglobin: 7.5%).

No history of smoking or alcohol consumption.

Preoperative Examinations

Imaging tests:

Carotid ultrasound (2 years prior to admission): Multiple plaques in the origin of the right internal carotid artery, 50–69% stenosis, and a 13.8 mm × 5.0 mm unstable hypoechoic plaque.

Cranial magnetic resonance imaging (MRI) (admission): Multiple acute cerebral infarctions in the right cerebral hemisphere, with multiple old ischemic infarcts (Figure 1).

Through cranial MRI, it was found that the patient's brain tissue contained multiple acute cerebral infarction lesions, mainly distributed in the right frontal lobe, basal ganglia, occipital lobe and other brain regions.

Computed tomography angiography (CTA) (admission): Severe stenosis (80%) at the origin of the right internal carotid artery, irregular vessel walls, and visible plaque shadows (Figure 2).

Through the patient's cranial CTA scan, it was found that there was severe stenosis (more than 80%) at the beginning segment of the right internal carotid artery.

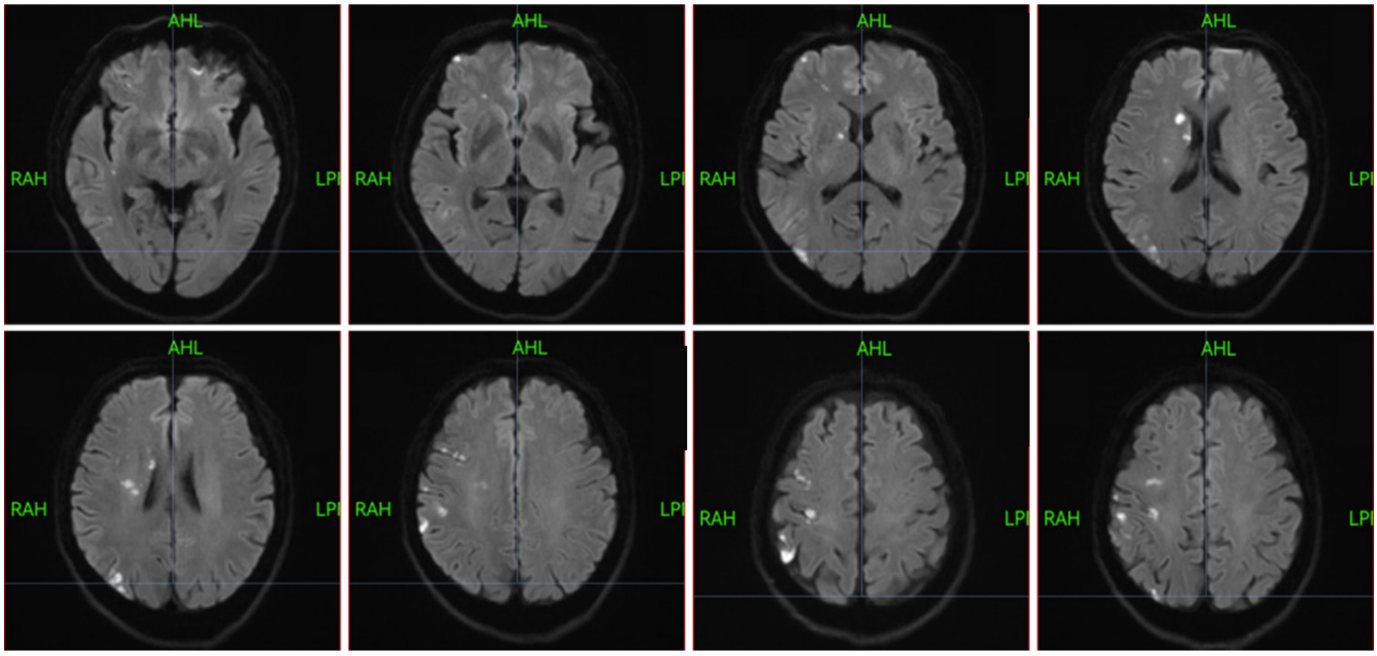
Other tests: Electrocardiogram (ECG) showing sinus arrhythmia and ST-T segment changes; blood tests confirming dyslipidemia and poor glycemic control.

Surgical Indications and Contraindications

Indications: Symptomatic severe carotid artery stenosis (80%) with recurrent TIAs, consistent with the 2017 Chinese Guidelines for the Diagnosis and Treatment of Carotid Artery Stenosis (symptomatic stenosis ≥50% for interventional treatment).

Contraindications: No absolute contraindications (e.g., active bleeding, severe coagulation disorders, or contrast agent aller-

Figure 1. Preoperative cranial MRI of the patient.



gy) were identified.

Surgical Instruments and Medications

Instruments: hydrophilic-coated loach guidewire, microguidewire, 8F guiding catheter, self-expanding nitinol stent (size-matched to the vessel), and distal filter-type EPD (matching the diameter of the distal internal carotid artery).

Medications:

Preoperative: Dual antiplatelet therapy (aspirin 100 mg/day + clopidogrel 75 mg/day) for 5 days.

Intraoperative: Atropine (for bradycardia), dopamine (for hypotension), and non-ionic contrast agent.

Postoperative: Continued dual antiplatelet therapy, nifedipine controlled-release tablets (for blood pressure), metformin + insulin (for blood glucose), and atorvastatin calcium tablets (for lipid regulation and plaque stabilization).

Surgical Procedure

Anesthesia: Local anesthesia (to monitor neurological function intraoperatively); Vascular access: Right femoral artery puncture using the Seldinger technique, followed by insertion of an 8F arterial sheath.

Guiding catheter placement: The guiding catheter was advanced to the common carotid artery (2 cm proximal to the lesion) under fluoroscopic guidance; EPD deployment: A shaped EPD was advanced to the distal C1 segment of the internal carotid artery under roadmap guidance and opened to fully cover the vessel lumen; Balloon angioplasty: A balloon (1–2 mm smaller than the internal carotid artery diameter) was used for pre-dilation of the stenotic lesion, followed by rapid deflation and withdrawal; Stent implantation: A self-expanding stent was advanced along the guidewire to the stenotic lesion, deployed, and post-dilated if necessary to ensure adequate apposition; EPD retrieval: The EPD (with intercepted emboli) was retrieved after confirming unobstructed blood flow and stable stent position via angiography; Intraoperative monitoring: Continuous monitoring of vital signs (heart rate, blood pressure) and neurological function.

Postoperative Follow-Up

Short-term: Postoperative DSA immediately after surgery; cranial CT on postoperative day 1; neurological examination and vital sign monitoring daily during hospitalization.

Long-term: 1-month follow-up including carotid ultrasound and assessment of symptoms (e.g., dizziness, TIAs).

Results

Intraoperative Findings

The surgery proceeded smoothly overall, with all steps completed as planned:

Vascular access: Successful one-time puncture of the right femoral artery; the 8F arterial sheath and guiding catheter were positioned correctly (parallel to the common carotid artery axis) without vessel injury.

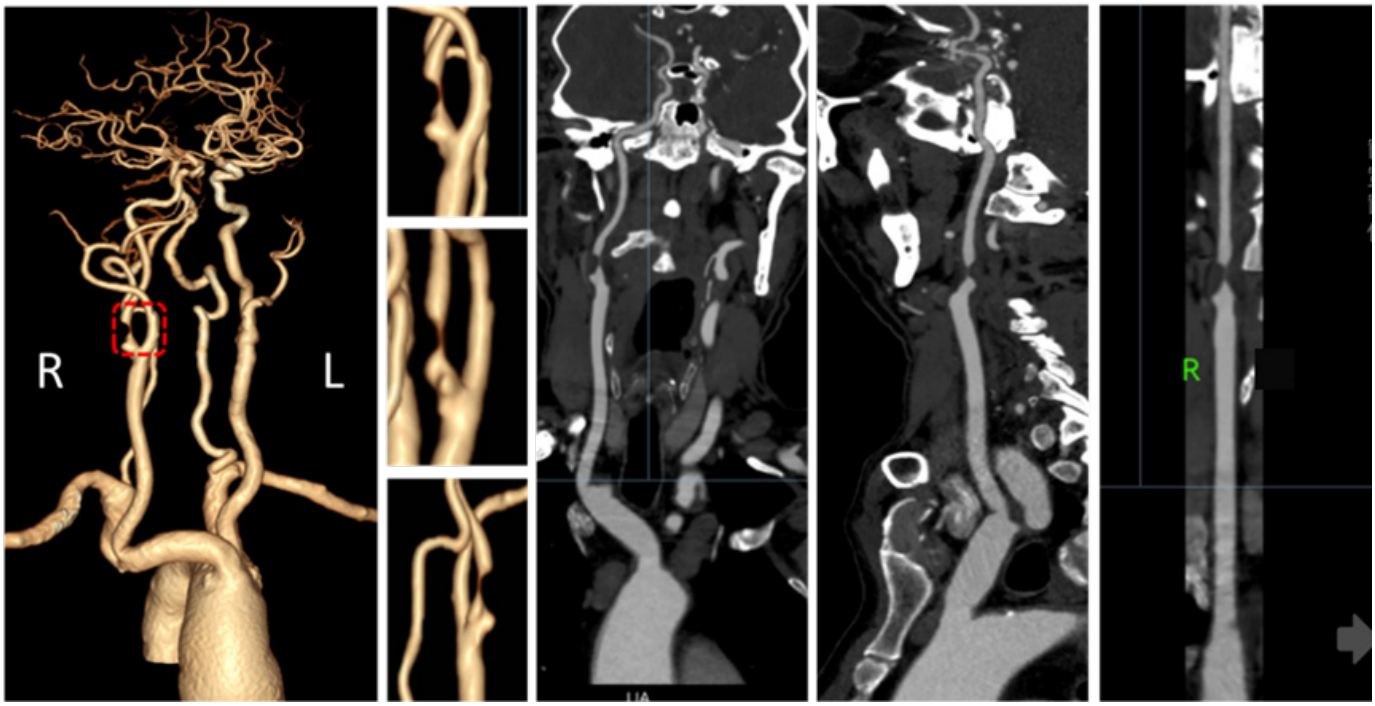
EPD deployment: The EPD was advanced through the stenotic segment without resistance, opened completely at the target "landing zone" in the distal C1 segment, and apposed closely to the vessel wall without displacement.

Balloon angioplasty: The balloon expanded fully in a cylindrical shape; post-angioplasty angiography showed significantly reduced residual stenosis, no dissection or thrombosis, and stable EPD position.

Stent implantation: The stent was deployed accurately, fully covering the stenotic segment with good wall apposition; post-deployment angiography showed residual stenosis <50%, no in-stent thrombosis, and normal vessel status.

Complication management: Transient bradycardia (minimum heart rate: 50 bpm) and hypotension (systolic blood pressure:

Figure 2. Preoperative cranial CTA of the patient.



90 mmHg) occurred after balloon angioplasty (attributed to carotid sinus reflex). Intravenous atropine (0.5 mg) and dopamine (2–5 μg/kg/min via intravenous pump) were administered, and vital signs stabilized within 5 minutes (heart rate: ~70 bpm, blood pressure: 120/70 mmHg).

Immediate Postoperative Outcomes

Postoperative DSA showed:

Accurate stent positioning at the origin of the right internal carotid artery, fully covering the lesion. Good stent expansion and close apposition to the vessel wall, with no gaps or displacement. Significant improvement in stenosis: Preoperative stenosis rate (80%) reduced to postoperative residual stenosis rate (<10%). Unobstructed blood flow: Increased contrast agent flow velocity through the stent segment, clear visualization of distal vessels, and good filling of branch vessels.

Postoperative Recovery

In-hospital recovery:

The patient returned to the ward in stable condition, with heart rate maintained at 70–80 bpm and blood pressure at 130–140/80–90 mmHg.

Postoperative day 1: Dizziness resolved; no recurrent TIAs; neurological examination showed improved biceps, triceps, and patellar reflexes; right Babinski sign turned negative; the patient could ambulate with assistance; cranial CT showed no intracranial hemorrhage or new cerebral infarction.

Postoperative day 3: The patient could ambulate independently and perform activities of daily living; continued dual antiplatelet therapy and management of comorbidities.

Postoperative day 7: No adverse symptoms; the patient was discharged.

1-month follow-up:

The patient reported complete resolution of dizziness and no recurrent TIAs; quality of life improved significantly. Carotid ultrasound showed unobstructed in-stent blood flow and no in-stent restenosis.

Discussion

Necessity and Advantages of CAS

CAS is a critical minimally invasive treatment for carotid artery stenosis, offering unique advantages for high-risk patients:

Minimally invasive nature: Compared with carotid endarterectomy (CEA)—a traditional open surgery requiring a large cervical incision and direct carotid exposure—CAS is performed via femoral artery puncture, with only a small puncture wound in the groin. This minimizes damage to normal cervical tissues and reduces the risk of CEA-related complications (e.g., cranial nerve palsy, wound infection, cervical hematoma) [7]. In this case, the patient (elderly with multiple comorbidities) tolerated CAS well, with no surgical site complications.

Rapid recovery: CAS has a shorter operative time and faster postoperative recovery than CEA. The patient in this case experienced reduced dizziness on the day of surgery, ambulated with assistance on postoperative day 1, and was discharged on day 7—far quicker than the typical 2–3-week recovery period for CEA [8]. This reduces hospital costs and improves patient quality of life.

Efficacy in stroke prevention: CAS restores blood flow by expanding the stenotic vessel with a stent, alleviating cerebral ischemia and reducing TIA and stroke risk [9]. Clinical studies (e.g., ACST-2, SPACE-2) have confirmed that CAS is non-inferior to CEA in preventing stroke in carotid stenosis, and may be superior in elderly or comorbid patients [10, 12]. This case further validates CAS efficacy: the patient's TIA recurrence ceased, and no new cerebral infarction occurred postoperatively.

Critical Role of EPDs in CAS

Mechanism of Embolus Interception

The distal filter-type EPD used in this case acts as a "mechanical barrier" to prevent embolic complications:

Structural design: The EPD consists of a fine metal mesh with precisely sized pores (small enough to trap lipid-rich emboli, large enough to allow normal blood flow). After deployment in the distal internal carotid artery, it forms a complete filter covering the vessel lumen.

Embolus capture: During balloon angioplasty or stent deployment, unstable atherosclerotic plaques may rupture, releasing lipid-rich emboli. These emboli are intercepted by the EPD's mesh and prevented from entering the cerebral circulation. Upon EPD retrieval, the captured emboli are removed from the body, eliminating the risk of cerebral embolism [13]. In this case, plaques were observed in the retrieved EPD, confirming successful embolus interception.

Reduction in Cerebral Embolism Risk

Cerebral embolism is a severe perioperative complication of CAS, with a reported incidence of 5–10% without EPD use [15]. EPDs significantly reduce this risk to 1–3% [16], as validated by clinical evidence:

A network meta-analysis by Giannopoulos et al. [16] showed that EPD use during CAS reduces the odds of perioperative stroke by 60–70% compared with no EPD.

In the CASWEP trial [15], patients undergoing CAS without EPD had a 3.2-fold higher cerebral embolism rate than those with EPD.

In this case, no cerebral embolism occurred, likely due to effective EPD use. Without EPD protection, the lipid-rich emboli intercepted during surgery could have caused new cerebral infarctions, leading to severe neurological deficits (e.g., hemiplegia, aphasia) and poor prognosis.

CAS Risks and Management Strategies

Common Risks

Despite its safety, CAS is associated with several risks:

Vascular perforation: Caused by excessive force during guidewire/catheter manipulation or mismatched instrument size, leading to hemorrhage and hematoma.

In-stent thrombosis: Related to hypercoagulability, platelet adhesion to the stent surface, or inadequate antiplatelet therapy [17-18].

In-stent restenosis: Occurs in 5–10% of patients within 1 year, due to intimal hyperplasia and smooth muscle cell proliferation [19-20].

Carotid sinus reflex: Triggered by balloon/stent stimulation of the carotid sinus, leading to bradycardia and hypotension (as observed in this case).

Contrast agent allergy: Manifesting as rash, pruritus, or severe anaphylaxis.

Puncture site hematoma: Caused by improper puncture tech-

nique or inadequate postoperative compression.

Prevention and Management

Vascular perforation: Preoperative vascular assessment (via CTA/MRI) to select appropriately sized instruments; gentle, precise manipulation during surgery. If perforation occurs, surgical intervention is required.

In-stent thrombosis: Preoperative dual antiplatelet therapy (≥5 days) to inhibit platelet activation; postoperative continuation of antiplatelet therapy for 6–12 months. For established thrombosis, thrombolysis or thrombectomy is recommended [18].

In-stent restenosis: Postoperative control of risk factors (hypertension, dyslipidemia, hyperglycemia); long-term statin use to stabilize plaques. Restenosis may be treated with repeat angioplasty or re-stenting [20].

Carotid sinus reflex: Preoperative atropine (0.5–1 mg) for high-risk patients; intraoperative monitoring of vital signs.

Contrast agent allergy: Preoperative allergy history inquiry; premedication with antihistamines/corticosteroids for high-risk patients. Severe anaphylaxis requires emergency treatment (e.g., epinephrine, corticosteroids).

Puncture site hematoma: Standardized puncture technique; 15–20 minutes of postoperative manual compression. Small hematomas are managed with cold compresses; large hematomas require surgical evacuation.

Conclusion

This case reports a 73-year-old male patient who developed severe stenosis of the initial segment of the right internal carotid artery due to high-risk factors such as long-term hypertension and diabetes, accompanied by frequent dizziness and transient ischemic attacks. After the lesion was confirmed through preoperative examination and met the surgical indications, carotid artery stent implantation was performed for treatment. During the operation, hydrophilic guidewires, 8F guiding catheters, self-expanding nitinol stents and distal filter-based EPD and other instruments were selected. The steps of establishing the puncture access, placing the EPD, balloon dilation, stent insertion and retrieval were completed in a standardized manner. Although transient bradycardia and hypotension occurred intraoperatively, vital signs were stabilized with intervention, and the procedure was completed successfully. Postoperative DSA showed that the stent position was accurate, the stenosis rate decreased from 80% to less than 10%, and the blood flow was unobstructed. The patient has recovered well, with alleviated dizziness, no recurrence of transient cerebral ischemia, improved neurological function and enhanced quality of life. During the one-month follow-up, carotid ultrasound showed that the blood flow within the stent was unobstructed and there was no restenosis. This case demonstrates the effectiveness and safety of the surgery, highlighting the crucial role of the EPD and providing a reference for clinical practice.

Abbreviations

CAS: Carotid Artery Stenting; TIA: Transient Ischemic Attack; EPD: embolic protection device; DSA: Digital Subtraction Angiography; CEA: Carotid Endarterectomy; MRI: Magnetic Resonance Imaging; CTA: Computed Tomography Angiography; ECG: Electrocardiogram; bpm: Beats Per Minute; ACST-2: Second Asymptomatic Carotid Surgery Trial; SPACE-2: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy-2; CASWEP: Carotid Artery Stenting Without Embolic Protection.

Acknowledgements

Not applicable.

Author Contribution

Ruixiao Yu, involved in drafting and finalizing the manuscript, and Chenlu Zhu, as the corresponding author, contributed to the study concept and supervision. All authors have approved the final version of the manuscript.

Funding Information

Not applicable.

Ethics Approval and Consent to Participate

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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