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JNND JOURNAL OF NEUROSCIENCE AND NEUROLOGICAL DISORDERS
ISSN 2639-3220

Research Article

Corticobasal Degeneration: A Review

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Submitted: October 28, 2025
Approved: November 08, 2025
Published: November 10 2025

How to cite this article: Membreno Lopez AS, Johnson S, Wax N, Cutchin C, May D, Curtain T, et al. Corticobasal Degeneration: A Review. J Neurosci Neurol Disord. 2025; 9(2): 072-079. Available from: https://dx.doi.org/10.29328/journal.jnnd.1001113

Keywords: Corticobasal degeneration; Tauopathy; Parkinsonism; Apraxia; Neurodegeneration

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Abstract

Corticobasal degeneration (CBD) is a rare neurodegenerative tauopathy characterized by progressive motor and cognitive dysfunction. This comprehensive review examines the clinical manifestations, neuropathology, diagnostic challenges, and management strategies for CBD. The disease presents with asymmetric motor symptoms, including rigidity, dystonia, myoclonus, and apraxia, often accompanied by cognitive impairments affecting executive function, language, and behavior. Neuropathologically, CBD is defined by 4-repeat tau protein accumulation in neurons and glial cells, producing characteristic lesions including astrocytic plaques and ballooned neurons. Diagnosis remains challenging due to significant clinical overlap with other tauopathies, particularly progressive supranuclear palsy, frontotemporal dementia, and Alzheimer's disease. Currently, no disease-modifying treatments exist; management focuses on symptomatic relief through multidisciplinary approaches, including physical therapy, occupational therapy, and speech-language pathology. This review synthesizes current understanding of CBD pathophysiology and highlights the urgent need for improved diagnostic biomarkers and targeted therapeutic interventions.

Introduction

Corticobasal degeneration (CBD) represents a rare but clinically significant neurodegenerative disorder first described in 1968 by Rebeiz et al. as corticodentatonigral degeneration with neuronal achromasia [1]. Originally characterized by progressive asymmetric motor dysfunction, CBD is now recognized as a complex tauopathy affecting both motor and cognitive domains [2,3]. The disorder belongs to the spectrum of 4-repeat (4R) tauopathies, distinguished by abnormal accumulation of hyperphosphorylated tau protein in neurons and glial cells [4].

The clinical presentation of CBD encompasses a broad spectrum of symptoms that evolve throughout the disease course. Motor manifestations typically include asymmetric rigidity, bradykinesia, dystonia, myoclonus, and apraxia, often accompanied by the distinctive alien limb phenomenon [6,7]. Cognitive and behavioral changes may precede motor symptoms by several years and include executive dysfunction, language impairment, and personality alterations [3,8]. This heterogeneous presentation significantly complicates diagnosis, as symptoms frequently overlap with other neurodegenerative conditions.

Understanding CBD pathophysiology has important implications beyond patient care. As one of several

tauopathies affecting the aging population, CBD research contributes to broader insights into tau protein dysfunction and potential therapeutic targets for related disorders [9]. This review synthesizes current knowledge regarding CBD epidemiology, pathophysiology, clinical manifestations, diagnostic approaches, and treatment strategies while identifying critical gaps in understanding that require future investigation.

Methodology

A structured and systematic literature search was conducted to identify relevant publications on corticobasal degeneration (CBD). The search was performed across multiple databases, including MEDLINE, PubMed, and Google Scholar, to ensure comprehensive coverage of peer-reviewed and publicly available research. The primary search period spanned January 2020 to October 2025, capturing contemporary developments in the epidemiology, neuropathology, clinical presentation, diagnostic methods, and management of CBD.

Search terms included combinations of keywords such as "corticobasal degeneration," "corticobasal syndrome," "CBD," "tauopathy," "neurodegenerative disorder," and "diagnostic criteria." Search terms were combined and adjusted to ensure comprehensive retrieval of relevant studies, and filters were applied to prioritize journal articles, systematic reviews, and meta-analyses. Case reports and conference papers were considered when they offered distinctive clinical insights or illustrated rare presentations.

Although recent literature formed the core of this review, selected earlier works were included to provide historical context and to address foundational legal and ethical considerations relevant to the discussion. Publications were selected based on relevance, scientific rigor, and contribution to the thematic scope of this review. While English-language articles were prioritized, non-English studies were included when they provided substantive data or perspectives and could be accurately interpreted. Reference lists of key works were also manually reviewed to identify additional pertinent sources not retrieved through database searches.

Epidemiology

Accurate epidemiological data for CBD remain limited due to diagnostic challenges and the disorder's rarity. Early clinicopathologic studies reported pre-mortem diagnostic accuracy ranges from 25% to 56%, significantly hampering population-based studies [10]. More recent analyses using advanced imaging and biomarker-based criteria continue to demonstrate low ante-mortem accuracy, though estimates have modestly improved with the use of consensus diagnostic frameworks [11]. Earlier epidemiologic estimates suggested an incidence suggest an incidence of approximately 1 per 100,000 individuals, with CBD representing 4% to 6% of Parkinsonian syndromes [2,10,12]. Current reports place the incidence between 0.6 and 0.9 per 100,000 per year, consistent with its recognition as a rare 4R tauopathy [2,10].

The typical age of onset occurs around 65 years, with a mean survival of approximately 5 years from symptom onset [3,6,10]. Contemporary cohort studies now indicate a broader age range (50–75 years) and a mean survival of 6–8 years, likely reflecting earlier recognition, improved supportive care, and diagnostic refinement [3,6]. Gender distribution appears relatively equal, although some studies suggest a slight male predominance at 53% [13]. These epidemiological uncertainties underscore the need for improved diagnostic criteria and biomarkers to enable more accurate population studies and natural history characterization.

Pathophysiology

Molecular pathology: CBD pathology is fundamentally characterized by abnormal accumulation of 4R tau protein in both neuronal and glial cells [4,5,14]. This pathological tau exists in hyperphosphorylated forms that disrupt normal microtubule function and cellular transport mechanisms. The preferential involvement of 4R tau isoforms distinguishes CBD from other tauopathies such as Pick disease, which primarily affects 3R tau [14].

Tau aggregation follows a prion-like spreading pattern through connected neural networks, beginning in striatal and anterior frontal regions before progressing to posterior cortical areas [15]. This spatial progression correlates with the clinical evolution from early motor symptoms to later cognitive and behavioral manifestations.

Neuropathological features: The characteristic neuropathological lesions of CBD include astrocytic plaques, coiled bodies within oligodendrocytes, and ballooned neurons, predominantly affecting cortical layers III, V, and VI [1,2,4,6,8,14]. Subcortical structures, particularly the striatum and substantia nigra, demonstrate significant tau deposition and neuronal loss, correlating with observed motor deficits [4,8,14].

Cortical atrophy in CBD typically presents asymmetrically, with greater involvement of the hemisphere contralateral to the more affected limb. However, when dementia or language difficulties predominate, frontal and temporal regions may show more symmetric involvement [1,6]. Affected cortical areas exhibit substantial gliosis and loss of normal cytoarchitecture [1,6,16].

Neuroinflammatory components: Emerging evidence suggests neuroinflammation plays a significant role in CBD pathogenesis. Tau aggregation activates microglia and astrocytes, leading to the release of pro-inflammatory cytokines and complement proteins [4,5]. This chronic inflammatory state may amplify neuronal injury and facilitate tau pathology spread through mechanisms

including microglial uptake and release of tau aggregates [4,6]. Markers of astrocytic activation have been identified in CBD and related tauopathies, suggesting inflammatory processes could serve as both diagnostic biomarkers and therapeutic targets.

Clinical manifestations

Motor symptoms

Motor dysfunction typically represents the earliest manifestation of CBD, reflecting the disease's predilection for motor cortex and basal ganglia structures. The hallmark presentation involves asymmetric limb rigidity and clumsiness, usually affecting one arm initially before progressing to other limbs [8,14].

Parkinsonism manifests as asymmetric or unilateral rigidity and bradykinesia, typically affecting the upper extremities. Tremor, when present, is usually high-frequency and action- or posture-related rather than the classic rest tremor of Parkinson's disease [1,2,6,14].

Dystonia affects approximately 80% of patients, characteristically presenting as involuntary muscle contractions in the upper extremities, often manifesting as a tightly clenched fist. Lower extremity involvement is less common [1,2,7].

Myoclonus frequently accompanies dystonia and is characterized by sudden, brief muscle jerks or spasms [1,2,6,17]. Current hypotheses suggest myoclonus results from hyperexcitability in the primary motor cortex [2,8].

Oculomotor abnormalities include impaired saccadic movements and other abnormal ocular movements, distinguishing CBD from typical Parkinson's disease [1,8,14].

Alien limb syndrome represents a distinctive feature wherein patients experience loss of motor control, sensation, and perception of the affected limb due to irregular contralateral parietal cortex activity and absence of visual feedback [1,2,8,14].

Apraxia constitutes a major clinical feature, characterized by the inability to perform voluntary movements of the upper extremities or oral structures despite intact motor strength and comprehension. Movement abnormalities in apraxia typically present distally and bilaterally, but can also affect the lower extremities, resulting in characteristic gait abnormalities [1.2.8].

Cognitive and behavioral symptoms

Cognitive impairments in CBD often precede motor symptoms by up to 8 years and significantly impact quality of life [17,18]. Common manifestations include executive dysfunction, amnesia, dyscalculia, abnormal sleep patterns, anxiety, depression, aphasia, and apathy [1,6,14,17,18]. More severe behavioral alterations may include compulsive and antisocial behaviors.

These cognitive symptoms reflect tau pathology's impact on the prefrontal cortex, basal ganglia, parietal cortex, and striatal regions [17,18]. The wide spectrum of cognitive manifestations contributes to diagnostic complexity and emphasizes the need for comprehensive neuropsychological assessment.

Genetics factors

While CBD is typically sporadic, genetic research has identified potential risk factors. The strongest association involves the MAPT gene on chromosome 17q21.3, which encodes tau protein [1,2,5,14,19]. The H1 haplotype appears more frequently in CBD patients compared to the general population, suggesting increased disease susceptibility [1,5].

Rare cases with CBD-like symptoms have been associated with mutations in genes linked to other neurodegenerative diseases, including PGRN and C9orf72 [1,2]. However, these likely represent phenotypic overlap rather than true CBD pathology.

Clinical presentation and diagnosis

Typical clinical course

CBD typically begins with subtle, asymmetric motor problems affecting one arm. Patients often report clumsiness, stiffness, or difficulty using the affected limb, sometimes progressing to the alien limb phenomenon [1,4,8]. As the disease advances, rigidity, bradykinesia, dystonia, and myoclonus develop, usually maintaining greater severity on the initially affected side. Postural instability and falls become common in later stages [6].

Concurrently with motor progression, many patients develop cortical dysfunction, including apraxia, language difficulties, and behavioral or cognitive changes [1,6,8,14,17,18]. This combination of progressive motor impairment with cortical signs creates CBD's characteristic clinical profile.

Diagnostic challenges

CBD diagnosis remains primarily clinical, lacking definitive biomarkers or diagnostic tests. The challenge is compounded by significant symptom overlap with atypical Parkinsonian syndromes, including progressive supranuclear palsy (PSP), Alzheimer's disease, frontotemporal dementia, corticobasal syndrome, and Parkinson's disease.

Current diagnostic criteria require asymmetric presentation, motor symptoms (rigidity, dystonia, myoclonus), and cortical signs (apraxia, alien limb phenomenon, visuospatial deficits) [1,2,4,8,14,17,18,20]. Cognitive and behavioral impairments affecting executive

function, language, memory, and personality are common as the disease progresses [1,2,4-6,8,14,17,18,20]. Minimum symptom duration is typically one year, with onset usually after age 50 [1,21-23].Neuroimaging Support

Neuroimaging can provide supportive diagnostic evidence. Magnetic resonance imaging may demonstrate asymmetric atrophy patterns [1,8,21]. Positron emission tomography imaging reveals metabolic and molecular changes in affected brain regions [1,8,21]. Tau PET imaging shows particular promise for differentiating CBD from other tauopathies [4,21]. Cerebrospinal fluid analysis represents an emerging biomarker approach requiring further validation [21] The relationship between clinical presentation, pathological findings, and neuroimaging features is summarized in Table 1 provides an integrated overview of the characteristic patterns observed in corticobasal degeneration.

Differential diagnosis

The diagnosis of CBD is complex due to the overlapping features with several neurodegenerative disorders. The compilation of motor symptoms, cortical dysfunction, cognitive and behavioral impairments, and pathology is often what leads to diagnosis. Misdiagnosis is unfortunately common for CBD. The following disorders are the most common differential diagnoses for CBD.

Progressive Supranuclear Palsy shares 4R tau pathology with CBD but presents differently, typically showing early postural instability, falls, rigidity, and cognitive dysfunction with a more symmetric presentation compared to CBD's asymmetry and limb apraxia [1,6,24].

Frontotemporal Dementia can overlap with CBD phenotypes, both demonstrating executive dysfunction, apathy, and disinhibition. However, classic FTD lacks asymmetrical motor findings characteristic of CBD [17,18]. Pick disease, a FTD subtype, involves 3R rather than 4R tauopathy and presents with early personality changes and less prominent motor symptoms [14].

Alzheimer's disease may resemble CBD when presenting with apraxia, visuospatial deficits, and language impairment [2,4,14,17,18]. Both diseases involve tau pathology, complicating differential diagnosis. Some clinically diagnosed corticobasal syndrome cases are found to have Alzheimer's pathology at autopsy [14].

Parkinson's disease shares Parkinsonian features with CBD, including asymmetric motor deficits, rigidity, bradykinesia, and tremor. Cognitive and behavioral symptoms, including executive dysfunction, apathy, and sleep disturbances, overlap between conditions [1,6]. Key differentiating factors include CBD's lack of response to levodopa therapy and presence of cortical signs [1].

Corticobasal syndrome (CBS) represents the most recognized clinical presentation of CBD, characterized by asymmetric motor signs, cortical sensory deficits, apraxia, and alien limb phenomenon [1,2,4,5,17,18,20]. Importantly, CBS can result from various underlying pathologies, including Alzheimer's disease, PSP, frontotemporal dementia, or Creutzfeldt-Jakob disease [2,4,14,17,18,20]. While CBS and CBD share clinical similarities, they are not synonymous entities. Table 2 provides a comparison of key differential diagnoses, including progressive supranuclear palsy, frontotemporal dementia, and Alzheimer's disease.

Diagnostic classification

International Classification of Diseases, 10th Revision (ICD-10) codes relevant to CBD include G31.85 (Corticobasal Degeneration), G31.9 (Degeneration of Nervous System, Unspecified), and related codes for differential diagnostic considerations.

Case studies analysis

Analysis of published case studies reveals significant diagnostic heterogeneity in CBD. Research demonstrates that patients with confirmed CBD experienced common symptoms including progressive asymmetric rigidity, apraxia, alien limb phenomenon, myoclonus, and dystonia, with pathology showing cortical ballooned neurons, frontoparietal neuronal loss with gliosis, and nigral and basal ganglia degeneration [25].

Notably, approximately 24% to 57% of clinically diagnosed CBS cases demonstrate CBD pathology at autopsy [25]. This discordance highlights the complexity of ante-

Table 1: Clinical, Pathological, and Imaging Correlates of Corticobasal Degeneration

Domain	Key Features	Underlying Pathology	Representative Imaging Findings
Motor	Asymmetric rigidity, bradykinesia, dystonia, myoclonus, apraxia, and alien limb phenomenon	Neuronal loss and gliosis in motor cortex, basal ganglia, and substantia nigra; 4R tau-positive astrocytic plaques and coiled bodies	Asymmetric frontoparietal cortical atrophy contralateral to the affected limb on MRI; hypometabolism in motor and parietal cortices on FDG-PET
Cognitive/Behavioral	Executive dysfunction, apathy, language disturbance, compulsive or antisocial behavior	Tau accumulation in prefrontal, parietal, and temporal cortices; ballooned neurons	Frontotemporal cortical atrophy; reduced metabolism on PET; abnormal connectivity on fMRI
Oculomotor	Impaired saccades, gaze apraxia	Brainstem and parietal tau pathology	Midbrain atrophy is possible on MRI
Sensory	Cortical sensory loss, neglect	Involvement of the posterior parietal cortex	Asymmetric parietal hypometabolism or atrophy
Neuroinflammatory	Microglial activation, gliosis	Tau-induced microglial response and cytokine release	Not visible directly; correlates with molecular imaging or CSF biomarkers under study

Table 2: Differential Diagnostic Comparison: CBD vs. PSP, FTD, and AD

Feature	Corticobasal Degeneration (CBD)	Progressive Supranuclear Palsy (PSP)	Frontotemporal Dementia (FTD)	Alzheimer's Disease (AD)
Primary Pathology	4R tauopathy with astrocytic plaques and ballooned neurons	4R tauopathy with tufted astrocytes	3R/4R tau or TDP-43 pathology	3R/4R tau and amyloid-β plaques
Motor Symptoms	Asymmetric rigidity, apraxia, dystonia, alien limb	Early postural instability, symmetric rigidity, vertical gaze palsy	Usually absent early	Late bradykinesia, mild Parkinsonism possible
Cognitive/Behavioral	Executive dysfunction, apathy, aphasia	Frontal disinhibition, slowed cognition	Early personality and behavioral change	Prominent episodic memory loss
Oculomotor Findings	Impaired voluntary saccades, cortical gaze apraxia	Vertical gaze palsy (especially downgaze)	Usually normal	Normal early
Imaging	Asymmetric frontoparietal atrophy	Midbrain atrophy ("hummingbird sign")	Frontal and/or anterior temporal atrophy	Temporoparietal and hippocampal atrophy
Key Distinguishing Feature	Marked asymmetry, cortical sensory loss, alien limb	Early postural instability and gaze palsy	Early behavioral disinhibition or aphasia	Prominent amnestic presentation

mortem diagnosis and the need for improved diagnostic criteria. Many patients receive an accurate diagnosis only post-mortem, emphasizing the critical importance of developing reliable biomarkers for living patients.

Emerging biomarkers

Recent advances in biomarker research have expanded understanding of corticobasal degeneration and improved the ability to diagnose and monitor the disease more precisely. The clinical presentation of CBD often overlaps with other neurodegenerative conditions, making fluid biomarkers increasingly useful to provide objective indicators of underlying pathology and disease progression.

Cerebrospinal fluid (CSF) tau proteins remain among the most studied indicators. Both total tau (t-tau) and phosphorylated tau (p-tau) reflect neuronal injury and abnormal tau accumulation [6,16,27]. In CBD, CSF tau elevations are usually modest and differ from the more pronounced increases seen in Alzheimer's disease, where the p-tau/t-tau ratio is higher [4,6,16]. This difference may help distinguish CBD from Alzheimer's and other amyloid-positive conditions. When analyzed together with amyloid-β, CSF tau results can improve diagnostic confidence and assist in differentiating CBD from other tauopathies [16,27].

Neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) have emerged as important blood plasma biomarkers that complement CSF analyses [16,28-31]. NfL, a structural component of neuronal axons, is released into plasma and CSF when axonal degeneration occurs. Elevated NfL levels in CBD correlate with greater cortical atrophy, faster functional decline, and more advanced disease stage [16,29,30]. Recent improvements in ultra-sensitive analytic platforms, such as single-molecule array (SIMOA) and advanced ELISA techniques, now allow precise measurement of plasma NfL and GFAP [30].

Additionally, GFAP, an intermediate filament protein produced by astrocytes, reflects astroglial activation and neuroinflammation [30,31]. Increased plasma GFAP has been reported in patients with corticobasal syndrome, particularly in amyloid-positive cases, suggesting that astrocytic reactivity may occur early in the disease process [28,30]. YKL-40, a glycoprotein secreted by activated astrocytes and microglia, has also shown potential as an indicator of inflammatory activity and disease progression [29,31]. Higher plasma NfL and GFAP levels have been associated with cortical thinning and reduced metabolism on imaging studies, reinforcing their role as markers of neurodegenerative burden and progression [29,30].

These biomarkers represent complementary aspects of CBD pathology. CSF tau reflects tau aggregation, NfL indicates axonal degeneration, and GFAP/YKL-40 reflect glial activation and inflammatory change. Their combined use enhances diagnostic accuracy, supports earlier disease recognition, and provides prognostic insight into the rate and severity of progression. Although overlap among atypical Parkinsonian syndromes remains a limitation, these findings mark meaningful progress toward biomarker-guided diagnosis and monitoring.

Treatment and management

Current therapeutic approaches

No disease-modifying treatments currently exist for CBD. Management focuses on symptomatic relief and maintaining quality of life through multidisciplinary approaches [32]. Since CBD symptoms overlap with other neurodegenerative diseases, patients often receive trials of levodopa for motor symptoms and cholinesterase inhibitors for cognitive problems, though responses are typically limited [21,33].

Physical therapy: Physical therapy interventions include dynamic and static balance exercises, stretching routines to prevent contractures, gait training, and resistance training to maintain muscle strength. The primary goal is to help patients maintain independence through interventions such as visual cueing, blocked practice, and posture correction [34-36]. Evidence suggests that regular exercise, including adapted tango programs, can improve disease-related motor symptoms and reduce fall frequency [35].

Occupational therapy: Occupational therapy focuses on fall prevention and safety during activities of daily living. A three-step framework emphasizes goal setting, activity analysis, and access to additional services [36]. Interventions

include providing adaptive equipment, environmental modifications (non-slip mats, grab bars), and simplified task strategies to reduce stress and fatigue [36].

Speech-language pathology: Speech-language pathologists address swallowing difficulties and the risk of aspiration pneumonia through techniques such as chin-tuck maneuvers, liquid thickening, paced feeding, and food texture modifications. Communication support may involve low-tech picture boards or high-tech speech-generating devices, along with cognitive-linguistic exercises for memory and word-finding difficulties [32].

Emerging therapeutic investigations: Research into nilotinib, an FDA-approved cancer drug that blocks specific proteins promoting cancer growth, shows promise for neurodegenerative diseases. Studies suggest nilotinib may reduce toxic protein accumulation and restore dopamine-producing neurons in Parkinson's disease [37-39]. Given shared pathophysiological mechanisms, similar approaches may benefit CBD patients, though clinical trials are needed to establish efficacy and safety.

Palliative care: The typical CBD management course follows three overlapping stages. Early-stage management emphasizes medications and therapies to maintain independence. Mid-stage care shifts toward safety and functional support with adaptive equipment and fall-prevention strategies. Late-stage management prioritizes palliative care, focusing on comfort, dignity, and caregiver support [32,40,41].

Future therapeutic directions

In recent years, research has begun to move beyond symptomatic management toward therapies that may slow or modify the disease course in CBD. Given that CBD is defined by abnormal accumulation of 4-repeat tau, current efforts have focused on reducing tau production, blocking aggregation, and limiting its spread between neurons [4,5,16].

One major direction involves tau-targeting immunotherapy. Monoclonal antibodies designed to bind extracellular or seeding-competent tau aim to neutralize toxic tau species and prevent their propagation within neural networks [4,5,16]. Although no antibody treatment has been approved for CBD, early studies in related tauopathies have shown reductions in tau pathology and improved neuronal integrity [5,6,34]. Key challenges remain, including ensuring adequate blood–brain barrier penetration and identifying the tau epitopes most relevant to 4R tauopathies [6,16].

Gene-based and molecular therapies are also attracting attention. Antisense oligonucleotides that reduce MAPT mRNA levels have shown promising early results in Alzheimer's disease and may be adaptable to CBD and other 4R tauopathies [4,6]. These approaches could theoretically lower the production of pathogenic tau isoforms and mitigate neuronal injury, though clinical translation is still in its early stages [5,6].

Repurposed small-molecule therapies, particularly nilotinib, have also been investigated for their potential neuroprotective effects. Originally developed as a leukemia treatment, nilotinib appears to enhance autophagic clearance of misfolded proteins and stabilize dopaminergic signaling [4,37-39]. While preliminary results are encouraging, larger studies are needed to determine whether these benefits translate into meaningful clinical outcomes in CBD [6].

The development of biomarker-guided clinical trials is essential to evaluate these emerging treatments. Combining tau PET imaging with plasma and CSF markers such as NfL and GFAP could help identify the most suitable patients and measure treatment response more precisely [6,16,34]. Integrating such objective markers into study design may help define optimal treatment timing and accelerate therapeutic discovery [4,6].

These developments reflect a gradual shift from palliative care to mechanism-based, biologically informed treatment in CBD. Continued collaboration between molecular research, biomarker science, and clinical trial design will be crucial to move closer to truly disease-modifying therapy [4,6].

Legal and ethical considerations

Diagnostic accuracy and clinical care

The high similarity between CBD and progressive supranuclear palsy creates significant diagnostic challenges, with clinical assessments achieving only 90% specificity [2]. This diagnostic uncertainty, combined with limited CBD-specific research, can lead to inappropriate clinical care and treatment decisions [2,21,40].

Neuropsychiatric manifestations

Early CBD symptoms, including cognitive impairment, alien limb phenomenon, impulsivity, hallucinations, and agitation, may be misinterpreted as psychiatric conditions [21,40]. This misinterpretation can lead to inappropriate antipsychotic treatment, which may exacerbate existing motor dysfunction [21].

Legal competency issues

CBD patients may experience symptoms affecting legal competency, including cognitive impairment, behavioral changes, and involuntary movements that could be misinterpreted as intentional actions [21,42]. Legal professionals must understand these disease manifestations when representing elderly clients, particularly given that approximately 60% of individuals with dementia or neurodegenerative conditions remain undiagnosed [42].

Determinations of fitness to stand trial require careful evaluation of cognitive function and understanding of CBD's impact on judgment and motor control. The insanity defense may be relevant when cognitive impairments affect the ability to form criminal intent (mens rea) [42,43].

Conclusion

Corticobasal degeneration represents a complex neurodegenerative disorder characterized by progressive motor and cognitive dysfunction resulting from 4R tau pathology. Despite advances in understanding its neuropathological basis, CBD remains diagnostically challenging due to significant clinical overlap with other tauopathies. The heterogeneous presentation necessitates comprehensive evaluation by experienced clinicians and highlights the urgent need for reliable biomarkers.

Current management relies on multidisciplinary symptomatic approaches, as no disease-modifying therapies exist. Physical therapy, occupational therapy, and speech-language pathology interventions can help maintain function and quality of life. Emerging therapeutic investigations, including studies of nilotinib and other compounds targeting tau pathology, offer hope for future disease-modifying treatments.

Future research priorities should focus on developing improved diagnostic criteria, identifying reliable biomarkers for ante-mortem diagnosis, and investigating the interplay between pathological changes, environmental factors, and genetic susceptibility. Enhanced understanding of neuroinflammatory mechanisms may reveal new therapeutic targets. Improved diagnostic tools and deeper mechanistic insights are essential for distinguishing CBD from related disorders and developing targeted interventions to alter the disease's relentless progression.

The clinical and research communities must work collaboratively to address diagnostic challenges, develop effective treatments, and provide comprehensive care for patients and families affected by this devastating condition. Only through such coordinated efforts can we hope to improve outcomes for CBD patients and advance our understanding of tauopathy-related neurodegeneration.

Declarations

Competing interests declaration: The authors declare that they have no competing interests.

Funding declaration: The authors received no financial support, grants, or funding for the research, authorship, or publication of this article.

Financial interests declaration: The authors have no financial or commercial interests that could be construed as a potential conflict of interest.

Ethical statement: This article does not contain any studies with human or animal participants, and informed consent is not required.

Use of artificial intelligence declaration: No generative artificial intelligence (AI) tools were used in the preparation, writing, or editing of this manuscript.

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