Corticobasal Degeneration: clinical and radiological aspects

Degeneração Corticobasal: aspectos clínico-radiológicos

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ABSTRACT

Corticobasal degeneration is a rare and slowly progressive neurodegenerative disorder that generally presents as atypical parkinsonism with early cognitive features. Classically, motor symptoms occur asymmetrically and include akinetic-rigid parkinsonism with dystonia and myoclonic jerks. Cognitive manifestations include apraxia, aphasia, cortical sensory deficits, and alien limb phenomenon. The terms corticobasal syndrome (CBS) and corticobasal degeneration (CBD) represent distinct conditions. The former denotes the clinical phenotype, whereas CBD can generally be confirmed by postmortem anatomopathological analysis. In clinical practice, it is often difficult to make a proper diagnosis because autopsy is rarely performed. Therefore, it would be desirable to develop biomarkers, such as neuroimaging, in this group of patients to establish a more accurate diagnosis. The data in the literature regarding magnetic resonance findings in CBS/CBD are conflicting; however, they remain the most widely used in clinical practice due to their greater availability. This report presents five cases of CBS, assessing clinical progress through motor and cognitive findings, correlated with neuroimaging.

Keywords: Corticobasal Syndrome, Corticobasal Degeneration, Neuroimaging, Tauopathies

RESUMO

A degeneração corticobasal é uma doença neurodegenerativa rara e de progressão lenta, que geralmente se apresenta como um parkinsonismo atípico com características cognitivas precoces. Classicamente, os sintomas motores ocorrem de forma assimétrica e incluem parkinsonismo rígido-acinético com distonia e mioclonias. As manifestações cognitivas incluem apraxia, afasia, déficits sensoriais corticais e o fenômeno do membro alienígena. Os termos síndrome corticobasal (SCB) e degeneração corticobasal (DCB) representam condições distintas. O primeiro refere-se ao fenótipo clínico, enquanto a DCB geralmente só pode ser confirmada por meio de análise anatomopatológica pós-mortem. Na prática clínica, é frequentemente difícil estabelecer um diagnóstico preciso, pois a autópsia raramente é realizada. Portanto, seria desejável o desenvolvimento de biomarcadores, como os de neuroimagem, nesse grupo de pacientes, para obter um diagnóstico mais preciso. Os dados disponíveis na literatura sobre os achados de ressonância magnética em SCB/DCB são conflitantes; no entanto, continuam sendo os mais amplamente utilizados na prática clínica devido à maior disponibilidade. Este relato apresenta cinco casos de SCB, avaliando a evolução clínica por meio dos achados motores e cognitivos, correlacionados à neuroimagem.

Palavras-chave: Síndrome Corticobasal, Degeneração Corticobasal, Neuroimagem, Tauopatias

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INTRODUCTION

Corticobasal degeneration (CBD) was first described as a distinct clinicopathological entity by *Rebeiz et al*. as "corticodentatonigral degeneration with neuronal achromasia," in 1968[1]. Two decades later, *Gibb* et al. introduced the term CBD, which is now widely used[2]. CBD is a rare, progressive, sporadic neurodegenerative disorder classified among atypical parkinsonian syndromes. The onset typically occurred between the 5th and 7th decades of life, with an average life expectancy of 7 years, equally affecting both sexes [3-6].

It is important to note that advances in neuropathological studies and clinical assessments have refined the concept of this disease. Although CBD classically presents as corticobasal syndrome (CBS), conceptually, they refer to different entities. CBS describes the clinical phenotype, whereas CBD is a neuropathological diagnosis typically established through postmortem examination[3-7].

The variability of clinical phenotypes in CBD, and different conditions pathologically related to CBS, makes the investigation of this group of neurodegenerative diseases challenging [5-8].

This article discusses the various clinical presentations and neuroimaging characteristics of corticobasal syndrome (CBS), illustrated in five case reports, as potentially useful tools for differential diagnosis. Furthermore, a literature review was conducted to deepen and update the understanding of this rare neurological condition.

CASE REPORT

Case 1: An 81-year-old man had impairment of walking, with falls within six months, and was wheelchair-bound for one year. Later, he also presented with hypertonia in the right upper limb. Concomitantly, he developed dysphagia and cognitive decline with loss of functionality and bradyphrenia. Levodopa was prescribed with no response. Neurological exam revealed restriction of vertical downward gaze, slow saccades, bradykinesia, and significant rigidity in the right upper limb and lower limbs, signs of frontal release, and involuntary elevation of the right arm with alien limb syndrome. The cranial MRI revealed global cortical atrophy, more pronounced in frontoparietal regions bilaterally, hippocampal atrophy (MTA 2), and midbrain atrophy.

Case 2: A 59-year-old woman experienced cognitive decline, with progressive memory loss and motor apraxia, five years ago. She could no longer perform previously learned household tasks and became dependent on activities of daily living, within two years of disease onset. Neurological exam showed severely impaired cognition with executive dysfunction, global aphasia, ideomotor apraxia, resting tremor in the right upper limb, polyminimyoclonus in both hands, rigidity and hyperreflexia in four limbs, with right Babinski and Hoffmann signs, gait apraxia, restriction of vertical upward and downward gaze, alien limb in the right upper limb, and signs of frontal release. The brain MRI revealed asymmetric frontoparietal atrophy, mostly on the left hemisphere.

Case 3: A 58-year-old woman complained of dyscalculia four years before, developing aphasia and progressive cognitive impairment, with severe executive dysfunction that left her disabled. Neurological examination revealed myoclonus, dystonic posture of the trunk and upper limbs, generalized hyperreflexia with bilateral Babinski sign, rigidity in all four limbs, gait apraxia, signs of frontal release, and severe cognitive impairment with pseudobulbar affect and little verbal interaction. Brain MRI revealed asymmetric frontoparietal atrophy, more pronounced on the left side, and bilateral hippocampal atrophy (MTA 2).

Case 4: A 68-year-old woman presented with dystonic movement and tremor of the right hand, three years before admission, followed by motor apraxia, cognitive decline, dysphagia, and dysarthria. Neurological examination showed a parkinsonian gait, myoclonus, generalized hyperreflexia, motor apraxia, aphasia, alien limb phenomena, and signs of frontal release. The brain MRI showed global parenchymal atrophy, more pronounced on the left frontoparietal cortex.

Case 5: A 64-year-old woman began to experience progressive difficulties in her work as a journalist in 2021, such as drafting articles and finding words when talking, becoming unable to do her job within 1 year. Within a few months, she developed tremors and stiffness in her right hand, as well as changes in balance and dizziness. She developed episodes of postural hypotension with syncope (tilt test revealed dysautonomia). On exam she presented postural instability, motor aphasia, agraphia, apraxia, rigidity, bradykinesia as well levitation of the right upper limb, slowed saccades, restriction of vertical conjugate gaze. Brain MRI revealed midbrain atrophy and abnormal parkinsonism index being 41.6 (NR ≤ 13.55).

TABLE 1: Clinical and Radiological Characteristics - Case Reports

Case	Age of onset	Clinical manifestations	Neuroimaging findings	MRI Pattern
1	79	Rigidity, difficulty walking, postural instability, cognitive decline, dysphagia, vertical gaze restriction, and alien limb syndrome	Global cortical atrophy, worse in the frontoparietal region, hippocampal atrophy, and midbrain atrophy	PSP
2	54	Cognitive decline, motor apraxia, executive dysfunction, global aphasia, resting tremor, rigidity, and alien limb syndrome	Asymmetric frontoparietal atrophy, worse on the left side	CBD
3	54	Cognitive impairment, myoclonus, dystonic posture, hyperreflexia, rigidity, gait apraxia, cognitive impairment, pseudobulbar affect	Asymmetric frontoparietal atrophy, bilateral hippocampal atrophy (MTA 2)	CBD
4	65	Difficulty walking, dysphagia, dysarthria, dystonic movement, aphasia, motor apraxia, parkinsonian gait, alien limb phenomena	Global parenchymal atrophy, worse in the left frontoparietal cortex	CBD
5	60	Cognitive decline, postural instability, motor aphasia, agraphia, apraxia, rigidity, bradykinesia, restriction of vertical conjugate gaze, alien limb phenomena	Midbrain atrophy and abnormal parkinsonism index	PSP

CASE 1:

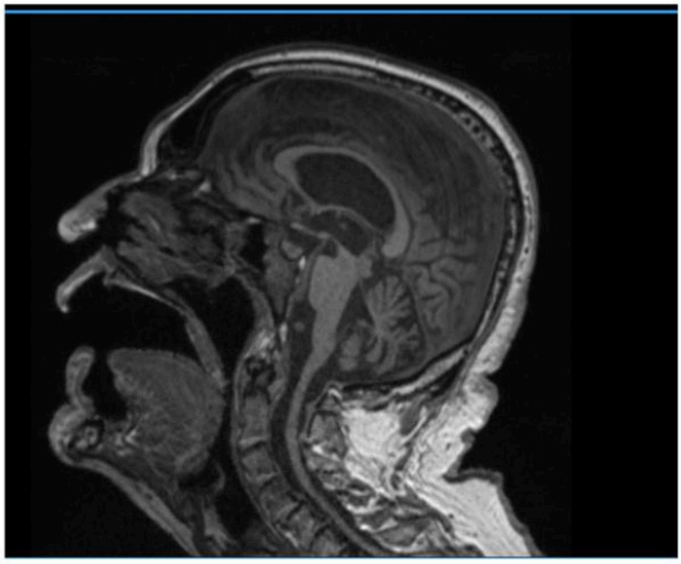

Fig 1- T1 Sagittal midline image: Atrophy of the midbrain (hummingbird sign).

CASE 2:

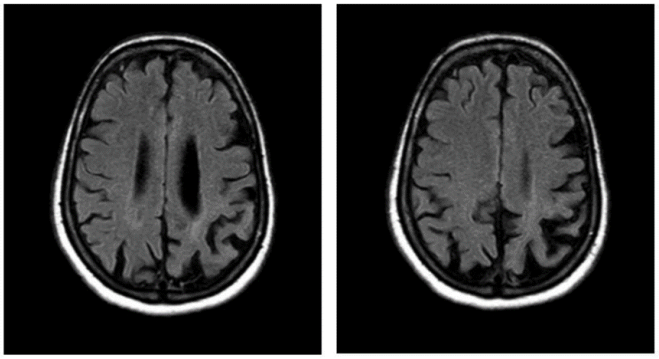

Fig 2 - Axial Flair: Asymmetric cortical atrophy, located in the superior parietal lobule, left postcentral gyri, without hyperintensity.

CASE 4:

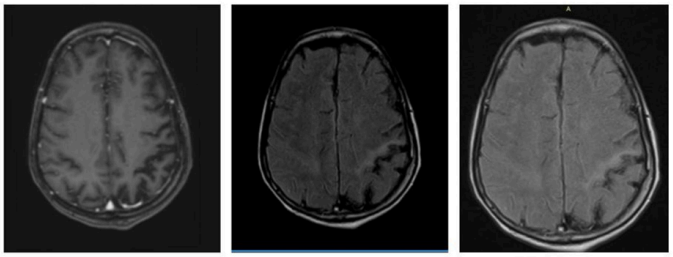

Figure 3 - Axial T1 (A) and Flair (B e C): Asymmetric atrophy of superior parietal lobule, perirolandic gyri, precentral gyri, postcentral gyri with hyperintensity.

CASE 5:

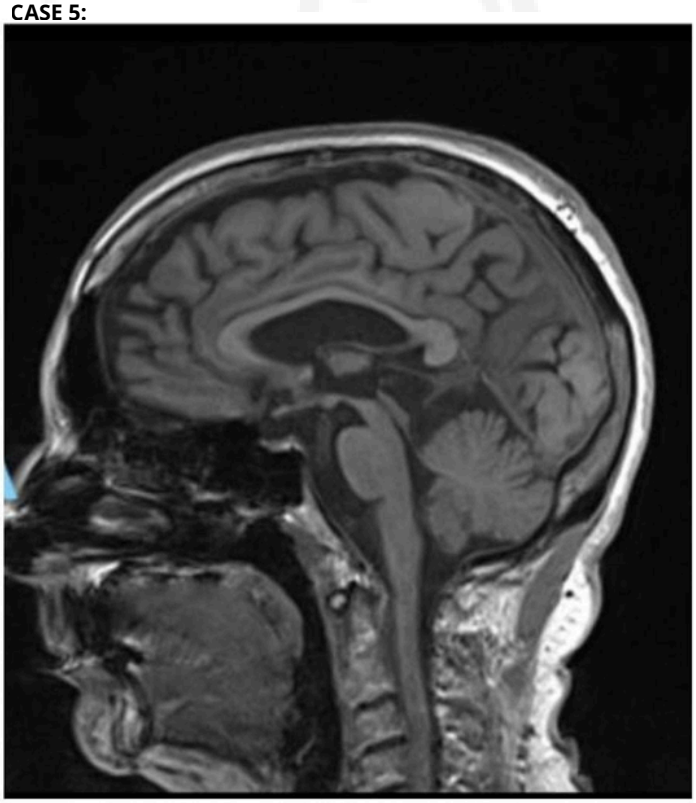

Figure 4 - Sagittal T1: Midbrain atrophy with Hummingbird sign.

DISCUSSION

Most neurodegenerative diseases affecting the central nervous system have a genesis involving incorrect folding of specific proteins. These proteins self-organize into oligomers and, ultimately, into insoluble fibrils, either intra- or extracellularly. The final consequence of this process is the death of nervous cells, leading to a progressive loss of brain function, manifesting as a series of clinical syndromes such as dementias, movement disorders, ataxias, and motor neuron diseases[6, 9].

The proteins commonly involved in neurodegeneration include beta-amyloid peptide, tau protein associated with microtubules, alpha-synuclein, TAR DNA-binding protein 43 (TDP43), and huntingtin[6, 10-12].

In a large group of neurodegenerative diseases known as tauopathies, abnormally hyperphosphorylated tau protein forms filamentous inclusions in neurons and, in some diseases, also in glial cells[6,12,13]. One of those

tauopathies is corticobasal degeneration (CBD), the subject of this article.

CBD classically presents as corticobasal syndrome, characterized by rigid-akinetic parkinsonism unresponsive to levodopa, asymmetric ideomotor apraxia, myoclonus, dystonia, cortical sensory loss, aphasia, progressive cognitive decline, and alien limb phenomena, reflecting involvement of the frontoparietal cortex, basal ganglia, and substantia nigra[5-7, 14].

Several other pathologies, such as progressive supranuclear palsy (PSP), Alzheimer's disease (AD), frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), Pick's disease (classified as a subtype of FTLD with tau protein inclusions), globular glial tauopathy type II, Creutzfeldt-Jakob disease, FTLD with FUS inclusions (FTLD-FUS), and multiple system atrophy (MSA), may clinically present as corticobasal syndrome [5, 6, 9-13, 15].

Similarly, CBD can manifest with different clinical presentations beyond the classic corticobasal syndrome (CBS). Clinical features and neuroimaging can assist in differential diagnosis.

In 2013, Armstrong and colleagues[3], based on autopsy studies from brain banks, proposed criteria to assist in the diagnosis of corticobasal degeneration, including five clinical phenotypes (syndromes) [table 2] associated with this underlying pathology, as well as definitions for probable and possible CBD[4] [table 3]

TABLE 2: Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration (Adapted from Armstrong et al. 2013)

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena
Possible corticobasal syndrome	May be symmetric: 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena
Frontal behavioral-spatial syndrome (FBS)	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia (NAV)	Effortful, agrammatic speech plus at least 1 of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, b) groping, distorted speech production (apraxia)
Progressive supranuclear palsy syndrome (PSPS)	3 of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

TABLE 3: Diagnostic criteria for corticobasal degeneration (Adapted from Armstrong et al. 2013)

	Clinical research criteria for probable sporadic CBD	Clinical criteria for possible CBD
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms	1 year	1 year
Age at onset	≥ 50 years	No minimum
Family history (2 or more relatives)	Exclusion	Permitted
Permitted phenotypes. (see table 2)	1) Probable CBS or 2) FBS or NAV plus at least one CBS feature (a-f)	1) Possible CBS or 2) FBS or NAV or 3) PSPS plus at least one CBS feature (b-f)
Genetic mutation affecting	Exclusion	Permitted

Typically, CBS involves asymmetric atrophy of the frontoparietal cortex, progressive loss of cortical volume and subcortical white matter, as well as atrophy of the corpus callosum and basal ganglia. Although these changes on magnetic resonance imaging (MRI) alone do not differentiate cases of CBS with or without underlying CBD[6, 14,16], some patterns might suggest an associated pathology.

Significant atrophy of the precentral and postcentral gyri in MRI, showing cortical involvement particularly affecting motor and sensory functions, points towards a diagnosis of CBD[17].

Hippocampal atrophy may be seen, often asymmetric and less prominent than in Alzheimer's disease[14,16]. When hippocampal atrophy is pronounced in a CBS patient, it could indicate a primary or co-existing AD pathology[17].

Furthermore, prominent midbrain atrophy, particularly when the hummingbird sign is present, due to selective midbrain volume loss with relative preservation of the pons, a reduced midbrain-pons ratio (0.52), and relative cortical preservation in early stages, strongly suggests PSP pathology underlying CBS[17,18], as seen in cases 1 and 5. These changes support the clinical diagnosis of PSP and help differentiate it from other parkinsonian syndromes[19-21].

MRI sensitivity in the early stages of CBS is relatively low, as changes can be subtle or absent. As disease progresses, MRI sensitivity increases but remains with low specificity, as other neurodegenerative disorders can overlap with CBS[16,17].

Positron emission tomography (PET) is useful for assessing metabolic and functional changes in the brain, as well as for detecting the accumulation of abnormal proteins, such as tau. In FDG-PET, characteristic hypometabolic patterns are observed asymmetrically in the frontoparietal regions and striatum. Hypometabolism can help differentiate CBD from other diseases, such as AD (which typically affects the temporal lobe) and PSP (which more prominently affects the midbrain and thalamus)[14,16-18,22].

PET-Tau can detect hyperphosphorylated tau accumulation, helping differentiate CBS resulting from CBD from CBS not associated with tauopathy. However, it is still unable to differentiate between tauopathies themselves[5,6,14,17].

Single-photon emission computed tomography (SPECT) is used to assess cerebral perfusion and dopaminergic function. In perfusion SPECT, asymmetric reductions are observed in the frontoparietal regions. Dopaminergic SPECT (SPECT-TRODAT) shows reduced uptake of ligands in the striatum, consistent with nigrostriatal degeneration observed in CBD[6,14,16]. Despite that, it does not help differentiate degenerative parkinsonian syndromes, as all of them have altered SPECT-TRODAT.

Neuroimaging is a useful tool in differential diagnosis, but confirmation, as already mentioned, comes

through anatomopathological changes.

Macroscopic investigation of CBD cases shows that cortical atrophy primarily affects the posterior regions of the frontal and parietal lobes, including the precentral and postcentral gyri. This atrophy is often asymmetric when CBD manifests clinically as CBS, being more severe on the opposite side to the most affected limbs[6,23]. There is ventricular dilation, reduction of white matter, thinning of the corpus callosum, flattening of the caudate nucleus, and discoloration of the globus pallidus, but atrophy of the subthalamic nucleus and midbrain, common in PSP, is rare or absent in CBD[6, 19-21,24].

Microscopic examination reveals neuronal loss, astrocytosis, and microvacuolization in the cerebral cortex, with abnormal neurons (Pick cells) often present. The reduction of subcortical white matter, including U fibers, is also a notable feature[5,25-27].Tau pathology, detected by immunohistochemistry, includes neurofibrillary tangles, pre-tangles, neuropil threads, and astrocytic plaques, which are pathognomonic features of the disease. These plaques are more abundant in premotor and prefrontal regions, as well as in the caudate nucleus. Tangles often deposit in diffuse regions of the cerebral cortex, globus pallidus, substantia nigra, hippocampus, amygdala, and dentate nucleus of the cerebellum[5, 25-28].

Pathologically, CBD can be divided into three subtypes based on the distribution and severity of lesions: “typical CBD”, “basal ganglia predominant CBD”, and “PSP-like CBD”. These subtypes generally correspond well to clinical phenotypes: “typical CBD” is associated with corticobasal syndrome (CBS) or frontal behavioral-spatial syndrome (FBS); "basal ganglia predominant CBD" and "PSP-like CBD" are associated with progressive supranuclear palsy syndrome (PSPS)[5,25-27]. In this context, we could classify some of the patients from the reported cases based on their clinical phenotypes into one of the pathological subtypes.

The patient in case 1 presented with striking features, gait disturbance with postural instability and falls, as well as vertical gaze palsy downward, motor apraxia, and alien limb phenomena. Brain MRI showed the characteristic hummingbird sign. Therefore, we could classify this patient as having CBS due to PSP pathology[19-21].

The other patients in cases 2 to 4, in turn, exhibited more pronounced cognitive impairment, such as motor apraxia, aphasia, alien limb phenomena, and executive dysfunction, which configure the clinical phenotype of classic CBS and, therefore, the pathological subtype of typical CBD.

The patient in case 5, on the other hand, clinically presented as CBS plus dysautonomia, confirmed by tilt test. Brain MRI revealed midbrain atrophy (hummingbird sign) and abnormal parkinsonism index (41.6), pointing to PSP as the underlying pathology[19-21].

Dysautonomia associated with CBS/CBD and PSP is very unusual, and when present, an extensive investigation is mandatory to rule out another condition generally related to dysautonomia, such as Multiple System Atrophy (MSA). However, in case 5, the motor phenotype was compatible with CBS and no changes suggestive of MSA were documented. When present, dysautonomia in tauopathies is generally mild, and it seems to be linked to parasympathetic system dysfunction, but its mechanisms are not yet fully understood[29,30].

From a genetic perspective, it is essential to understand the mechanisms underlying toxic tau protein accumulation, as they may be future targets for disease-modifying treatments.

Primary tauopathies are diseases in which tau pathology is the main contributing factor or hallmark feature (CBD, PSP, FTLD, Pick’s disease, and globular glial tauopathy). Tau protein plays a crucial role in regulating essential neuronal processes, such as microtubule stabilization, axonal transport, and synaptic plasticity[31,32].

It is encoded by the MAPT gene, which consists of 11 exons and is located on chromosome 17, with 6 isoforms in the adult brain (0N3R, 0N4R, 1N3R, 1N4R, 2N3R, and 2N4R) [5,31-36]. Exons 2, 3, and 10 are the main targets of alternative splicing, a process responsible for generating different forms of protein (isoforms) from the same gene[13,31-36]. The tau isoforms differ by having zero, one, or two insertions of 29 amino acids at the N-terminal (0N, 1N, or 2N - exons 2 and 3) and three or four repeated regions at the C-terminal (3R or 4R - exon 10)[31-36].

The ratio of 3R to 4R tau isoforms is crucial for normal neuronal function, and imbalances are linked to the accumulation of hyperphosphorylated tau, generating insoluble aggregates, which are the genesis of tauopathies[13,31-36]. More than 70 variants of the MAPT gene have been reported to cause several types of tauopathies[5,13,32-36].

In addition to changes in the MAPT gene, familial cases with a clinical phenotype of CBS and FTLD-TDP pathology, resulting from mutations in the progranulin gene (GRN) or the C9orf72 gene, have also been documented[5,6,37-40]. However, they are rarely associated with CBD pathology.

CONCLUSION

In recent decades, advances in the study of neurodegenerative diseases have been significant, with new knowledge about genetics, biomarkers, clinical progression and neuroimaging. However, CBD still represents a diagnostic challenge due to the multiplicity of clinical phenotypes and the absence of specific pharmacological therapy.

Understanding the underlying pathological mechanisms, including protein accumulation and neuronal dysfunction, is crucial for developing new diagnostic techniques and effective therapeutic strategies to modify the disease course.

Using tools such as neuroimaging features may be a useful strategy for assisting in the pathological diagnosis of corticobasal syndrome. More research is needed to elucidate the genetic and environmental factors contributing to this condition and explore new diagnostic and therapeutic approaches that may slow disease progression.

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