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Review Article

The Essentials in Corticobasal Degeneration

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Abstract

Diseases that affect the basal nuclei are characterized by slowness and a reduction in the range of movement (bradykinesia-hypokinesia), often associated with tremor, rigidity, and postural alterations. The term 'parkinsonisms' refers to these findings, the most common etiology of which is Parkinson's disease (PD). There are akineto-rigid parkinsonisms, especially without tremor, that do not respond to L-dopa and correspond to one of these three neurodegenerative disorders: 1) progressive supranuclear palsy (PSP), 2) multiple system atrophy (MSA), or 3) corticobasal degeneration (CBD). Each of them has characteristic signs and symptoms that distinguish them from PD, but these may not be present at the beginning of the disease. These conditions usually do not respond to dopaminergic drugs and must be addressed correctly in the early phase. The main problem is that patients with typical clinical signs and symptoms of PD can have very diverse pathologies, and patients with the same pathology can have different clinical signs and symptoms (atypical parkinsonisms with typical or atypical presentation). Recently, interest has grown in the knowledge of these diseases, characterized by abnormal intracellular accumulation of misfolded proteins, such as tau (PSP and CBD) and α-synuclein (MSA). Knowledge of the characteristic signs and symptoms of PSP, MSA, and CBD is essential for the adequate diagnostic and therapeutic management of patients suffering from atypical parkinsonisms. CBD is a rare entity. In the present work, we will develop the clinical characteristics and various treatment options in clinical practice.

Keywords: *Parkinsonisms; Corticobasal Degeneration; Diagnosis; Treatment*

Introduction

Corticobasal degeneration (CBD) constitutes a progressive neurodegenerative disease accompanied by asymmetric parkinsonism and cognitive impairment [1]. It is part of the group of tauopathies and is due to an abnormal intracellular accumulation of the misfolded tau protein. Histopathological examination by necropsy allows for an unequivocal diagnosis of the disease [2]. CBD must be differentiated from corticobasal syndrome (CBS), characterized by cognitive impairment and movement disorders, associated with asymmetric atrophy

of the fronto-parietal perirolandic cortex and the basal nuclei (substantia nigra and GPi-striatum). Although CBD constitutes the main cause of CBS, other conditions can mimic it, namely: 1) progressive supranuclear palsy (PSP), 2) Alzheimer's disease (AD), 3) fronto-temporal dementia (FTD), and 4) Lewy body disease (LBD). When multiple entities coexist with the same syndrome, the clinical diagnosis of CBD is difficult [3].

History

Rebeiz, Kolodny, and Richardson (1968) described CBD for the first time. They reported three clinical cases of patients with motor and posture abnormalities. The existence of bradykinesia, tremor, dystonia, rigidity, lack of motor dexterity, numbness of a limb, and gait disorders stand out. They called this clinical condition "cortical basal ganglionic degeneration (CBGD), based on the anatomical-pathological findings of the patients, where asymmetric fronto-parietal cortical atrophy, loss of neurons in the substantia nigra (SN), and edematous neurons were evident (achromatic cells) [4]. The term CBD was first coined by Gibb, Luthert, and Marsden (1989) when describing another series of similar cases [5].

Epidemiology

CBD is a rare neurological entity, with an incidence of less than 1/100,000 inhabitants/year. It represents 4 - 6% of patients with parkinsonism [3]. Most cases are sporadic, although some familial cases have been reported [6]. The average age of onset of symptoms is from the sixth decade, with the youngest case reported being 43 years old. There are no major differences in prevalence in relation to sex, and there are no known racial and/or ethnic factors [2]. No environmental factors (toxic or infectious agents) associated with CBD are reported [1]. A geographical grouping of tauopathies has been described, in favor of environmental factors that could be relevant in their genesis [6].

Clinical picture

CBD is a movement disorder associated with cognitive deficits [7]. The classic presentation is included within CBS, characterized by progressive motor and cognitive alterations. However, other phenotypes are recognized, such as spatial and behavioral frontal syndrome (BFS), a non-fluent agrammatical variant of primary progressive aphasia (PPA), and PSP syndrome [9] (Table 1). The clinical manifestations of CBD result from cortical and basal nuclei involvement. Motor manifestations include asymmetric parkinsonism, dystonia, myoclonus, postural instability, and falls. Behavioral manifestations include aphasia, apraxia, the alienated limb phenomenon, and parietal cortical anesthesia, as expressions of the most representative cortical signs [10].

Syndrome	Diagnostic criteria
Probable CBS	Asymmetric presentation of at least two of the following criteria: rigidity and/or bradykinesia in a limb, dystonia and/or myoclonus, in addition to at least two of the following criteria: buccal apraxia or limb apraxia, cortical sensory deficit, and the phenomenon of an alienated limb.
Possible SCB	Symmetric or asymmetric presentation of one of the following criteria: rigidity and/or bradykinesia in a limb, dystonia and/or myoclonus, in addition to one of the following criteria: buccal apraxia or limb apraxia, cortical sensory deficit, and the phenomenon of an alienated limb.
FBS	Presentation of two of the following criteria: executive dysfunction, behavioral or personality changes, and visuospatial deficits.
PPA nf	Non-fluent elocution, characterized by forced and ungrammatical speech, in addition to one of the following criteria: difficulty in understanding sentences with the preservation of understanding isolated words, or apraxia of speech.
PSP	Presentation of three of the following criteria: axial or symmetrical rigidity or bradykinesia of both limbs, postural instability or repeated falls, dystonia, urinary incontinence, behavioral changes, supranuclear vertical conjugate gaze palsy, or slowing of saccadic movements in the axis vertically, usually downwards.

Table 1: *Clinical diagnostic criteria for CBS.*

Motor symptoms

Parkinsonism

Parkinsonism can manifest itself in various ways, the most characteristic being an akineto-rigid, asymmetric, or unilateral form [9], although isolated cases of bilateral and symmetric presentation have been reported [10]. The patient may present rigidity, bradykinesia, tremor, and postural instability, associated with gait disorders [9]. The tremor is atypical, usually high frequency (greater than 6 Hz) and, unlike idiopathic Parkinson's disease (PD), of the postural or action type [10].

Dystonia and myoclonus

At the beginning of the disease, most patients develop dystonia, accompanied by myoclonus. They mainly involve the upper limbs and rarely the lower limbs and eyelids (blepharospasm) [9,10]. A typical position is that of a closed fist, which is usually accompanied by pain [9].

Oculomotor disorders

CBD is associated with oculomotor involvement, which makes differential diagnosis with PSP difficult. A difficulty or delay in conjugate gaze is usually observed, at the beginning of saccadic movements, in the horizontal axis, such as the case of CBD, and in the vertical axis (PSP), although uncommon [1].

Non-motor symptoms

Gradual cognitive deterioration constitutes the most frequent clinical manifestation of cortical dysfunction due to asymmetric fronto-parietal involvement. Even this may be the only form of presentation of the disease.

Executive dysfunction and behavioral changes

The patient may present behavioral, personality, and judgment changes, failures in planning, amnesia, and dyscalculia. Among the behavioral alterations, compulsive, bizarre, and antisocial behaviors, irritability, disinhibition, apathy, depression, and anxiety are observed. Hypersexuality and compulsive eating behaviors have been described (Kluber and Bucy) [9]. This set of signs and symptoms, associated with visuospatial alterations, comprises one of the possible phenotypes of CBD presentation, fonto-basal syndrome (FBS) [9,10].

Aphasia

Patients with aphasia present forced, ungrammatical, and non-fluent speech, preserving the understanding of isolated words, with difficulty in understanding complex sentences, manifesting as a non-fluent PPA syndrome [9].

Apraxia

Apraxia is observed in the upper and lower limbs and at the oral level. In the upper extremities, apraxia is usually bilateral and distal, making it difficult to imitate hand gestures (intransitive movements) and manipulate objects (transitive movements). On the other hand, at the level of the lower limbs, it presents as difficulty in starting to walk (gait apraxia) and an increased risk of falls [1,10].

Alienated limb phenomenon

Limb alienation is a classic sign of CBS, reflecting dysfunction of the contralateral parietal cortex [2]. It is defined as the subjective feeling of strangeness of a member that takes on its own will. There are two possible variants for this phenomenon: 1) the posterior or sensory variant, which is related to sensory hemineglect. The typical example is levitation of the upper limb, which can be initiated by

tactile stimuli; 2) the anterior or motor variant is characterized by involuntarily catching different body segments, clothing, furniture, and even people around them [9]. Many patients are not aware of these movements or if they are, they generate feelings of disgust and/or rejection [9,10].

Cortical hypoesthesia

It is characterized by numbness and paresthesia of a limb, associated with the alienated limb phenomenon. Loss of epicritic discrimination, agraphoesthesia, asterognosia, and stimulus extinction phenomenon can be observed [1]. The loss of epicritic discrimination results in the inability to differentiate two specific stimuli applied in close proximity. Agraphoesthesia is defined as the inability to recognize letters or numbers written on the skin. Asterognosia is the loss of the ability to identify and recognize the shape and nature of an object through palpation, in the absence of a visual stimulus. The phenomenon of stimulus extinction is the defect in recognizing the same stimulus applied simultaneously in two symmetrical areas of the body. Cognitive functions can be evaluated by asking the patient to perform a series of tests with his eyes closed, namely: 1) a sharp object can be used (Weber's compass) and ask him to indicate when he feels that he is being touched in two different sites, evaluating discrimination commitment; 2) a letter or number can be written on the palm of the hand and/or pad of the fingers and ask the patient to recognize it, and thus evaluate agraphoesthesia; 3) [9], to reveal asterognosia, the patient is given an object and asked to identify it; 4) to objectify the phenomenon of stimulus extinction, the patient must be touched on the back of both hands simultaneously and then separately, repeating this action repeatedly and interspersed, asking the patient if he recognizes when he is being touched in one or two hands.

Pre-motor symptoms

Regardless of the motor condition, behavioral changes, executive dysfunction, and language alterations constitute the central symptoms of CBD and frequently manifest at the onset of the disease. In this way, these non-motor symptoms may precede the appearance of motor symptoms, which present late [11].

Genetics and pathology

Neuropathological and genetic studies demonstrate that the microtubule-associated protein tau plays a pathogenic role in CBD (Figure 1). Pathologies in which the dysfunction of this protein is the determining factor in pathogenesis are referred to as "tauopathies". Different biochemical profiles of tau protein isoforms exist, depending on whether there are three or four repeats in the microtubule-binding domain, known as 3R or 4R, respectively. CBD is a 4R tauopathy, as are other neurodegenerative diseases like PSP and variants of FTD [7]. Mutations in the MAPT gene, which encodes microtubule-associated protein tau highly expressed in central nervous system cells, might be linked to the dysfunction of tau. This gene is located on chromosome 17q21.3 and is essential for microtubule assembly and stability [7]. Mutations in MAPT could lead to post-translational modifications of tau, primarily hyperphosphorylation [6]. However, the cellular mechanism underlying tau hyperphosphorylation remains unknown. The presence of hyperphosphorylated tau could reduce its affinity for microtubules, leading to microtubular functional alterations, either a loss or gain of function. Disassociated tau protein would have a higher tendency to polymerize, forming neurofibrillary inclusions in neuroglial cells and neurons, with astrocytes being the first to be affected [2,7] (Figure 2). Microglial involvement plays a crucial role in the pathogenesis of CBD. A molecular biology study from 2010 describes a mechanism by which altered microglial signaling leads to neuronal inflammation and, consequently, tau hyperphosphorylation [7]. In addition to MAPT gene mutations, an increased frequency of expression of the H1 haplotype of the MAPT gene is observed in CBD patients [6,7]. Mutations in the gene encoding progranulin (PGRN), mutations in the LRRK2 kinase, and mutations in myelin-associated oligodendrocytic basic protein (MOBP) have also been described. Many of these mutations are also present in PSP [2,8]. The neurodegenerative process occurs as a result of tau protein inclusions. Macroscopically, there is asymmetric atrophy of the fronto-parietal cortex and the basal ganglia. Histologically, the following features are observed: 1) astrocytic plaques, 2) spongiosis, 3) abaloned and achromatic neurons, and 4) oligodendrocytes in coils. Inclusions affect the cerebral cortex, basal ganglia, diencephalon, and

brainstem (Figure 3). The spatial distribution of these inclusions in the central nervous system determines the clinical presentation in the patient [3,7]. These findings contribute to the diagnosis of CBD, and at times, they can overlap with those observed in PSP, making the differential diagnosis between CBD and PSP challenging [2,7].

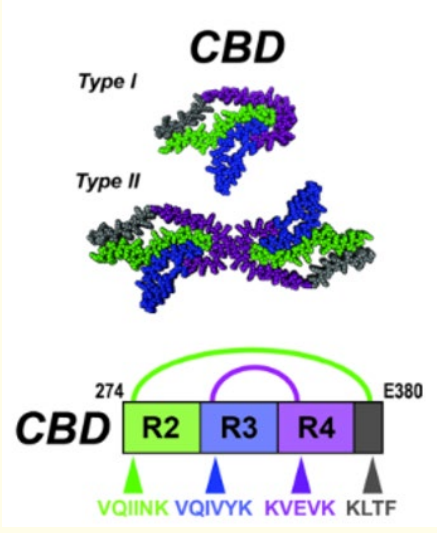


Figure 1: *Cryo-electron microscopy image of tau protein in CBD. The structure is spatially represented and colored according to the repeat domains. The structure was divided into two types: type 1 with a single protofilament and type 2 with two protofilaments, related by a C2 symmetry [18].*

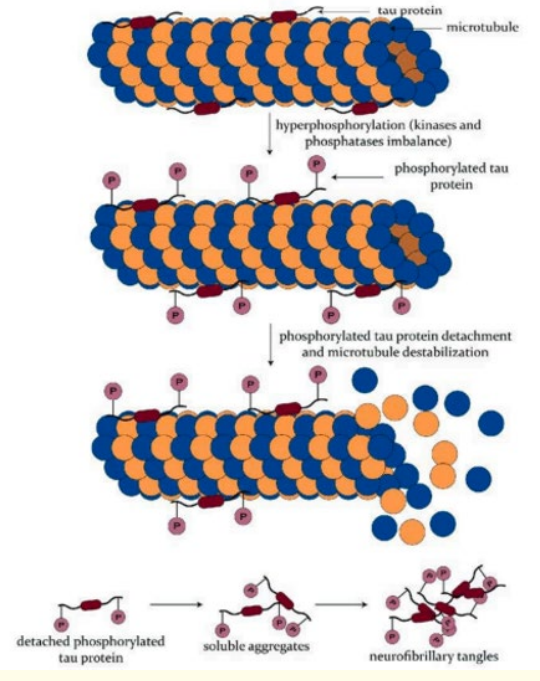


Figure 2: *Formation of neurofibrillary inclusions. Normally, tau protein functions as a microtubule-associated protein. Under pathological conditions, tau protein becomes hyperphosphorylated, destabilizing the microtubule through its dissociation. Phosphorylated tau protein binds together to form neurofibrillary inclusions [15].*

Major criteria	1. Neuronal and glial lesions with tau pathology. Filamentous lesions and astrocytic plaques in gray and white matter associated with prominent tau immunoreactivity in cellular processes. 2. Tau-immunoreactive lesions in the caudate and putamen nuclei. 3. Marked neuronal loss (depopulation) in the substantia nigra. 4. Neuronal depopulation and cortical astrogliosis (typically more pronounced in the upper frontal, upper parietal and pre- and post-rolandic gyri).
Supporting criteria	1. Retraction (atrophy) of parasagittal and perirolandic cerebral cortex associated with posterior frontal retraction, cortical spongiosis, thinning of the corpus callosum, retraction of the head of the caudate, decreased thalamic volume, and pallor of the substantia nigra. 2. Achromatic or abaloned neurons. 3. Neurofibrillary lesions in monoaminergic nuclei of the brainstem (locus coeruleus and substantia nigra), formerly known as corticobasal bodies. 4. Tau-positive argyrophilic inclusion bodies in oligodendrocytes, referred to as coiled bodies. 5. Preservation of the hippocampal and parahippocampal gyri.
Exclusion criteria	1. Senile plaques and Alzheimer-type neurofibrillary tangles. 2. Pick bodies with clearly defined margins. 3. Intracellular Lewy bodies (alpha-synuclein pathology). 4. Ubiquitin immunoreactivity. 5. Focal ischemic or hemorrhagic vascular lesions.

Table 2: *CBD. Anatomopathological diagnostic criteria [21].*

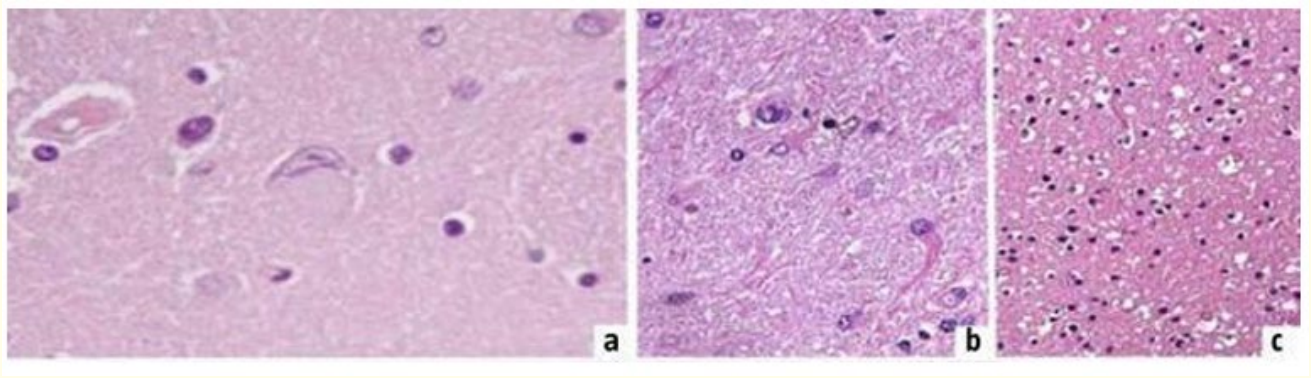


Figure 3: *CBD. Histopathology. a) 'Abaloned' neurons with eccentric nuclei and Nissl substance dispersion (H/E, 63×); b) Marked neuronal loss and astrocytic gliosis in the mesencephalon (H/E, 40×); c) Neuronal loss and focal spongiosis in the frontal cortex (H/E, 20×); d) Astrocytic plaque, a characteristic feature of corticobasal degeneration, representing tau accumulations in the distal segments of astrocytes (AT8, 40×); e) Intraneuronal deposits of phosphorylated tau (AT8, 40×); f) Deposits of phosphorylated tau forming 'neuropil threads' (AT8, 40×).*

Complementary exams

Brain magnetic resonance imaging (MRI)

Cerebral MRI reveals cortical retraction associated with accentuation (widening and deepening) of cortical sulci on the fronto-parietal convexity, which is asymmetric and contralateral to the affected body hemisphere. This finding, indicative of atrophy, may extend to the hippocampal regions, the superior temporal gyrus, and the striatum [16].

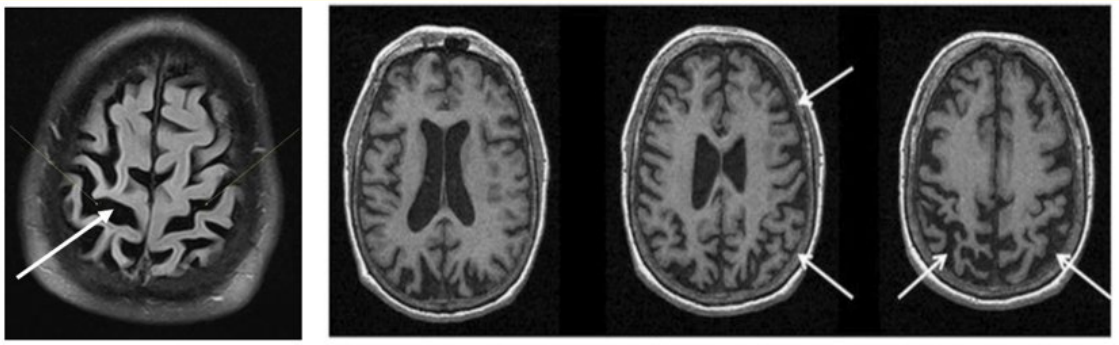
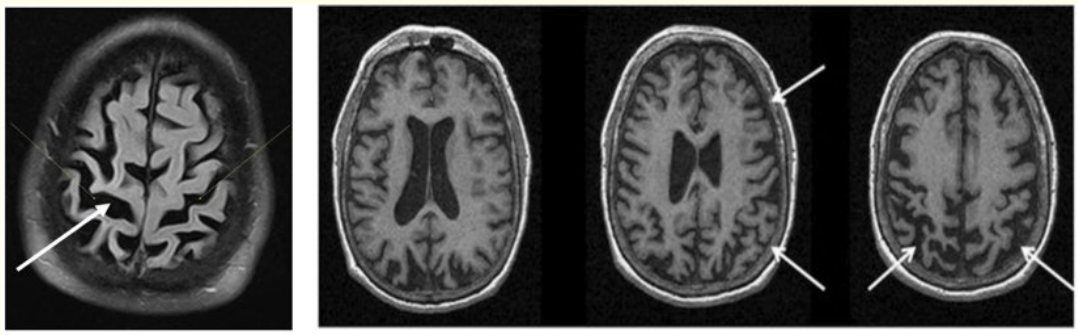


Figure 4: *MRI Image, axial T1-weighted sequence, of a patient diagnosed with CBD, confirmed by pathology. The series of axial T1-weighted slices reveals bilateral, asymmetric fronto-parietal cortical retraction, predominantly affecting the right cerebral hemisphere (white arrows) [16].*

Positron emission tomography

PET-CT is used after the intravenous administration of fluorodeoxyglucose (FDG). In CBD, a bilateral, asymmetric hypometabolism of the fronto-parietal cortex, thalamus, and the basal ganglia region is observed, contralateral to the clinically more affected body hemisphere.



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Hypometabolism in the parietal cortex allows differentiation between CBD and PSP [16].

DAT SPECT

Uptake of the dopamine presynaptic transporter (DAT) is typically abnormal in patients with CBD. However, involvement of the substantia nigra (SN) often occurs in advanced stages of the disease, so a normal finding in this type of study does not rule out the diagnosis of the disease [6].

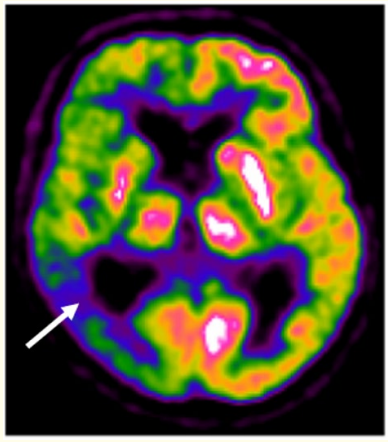

Figure 5: *A 76-year-old patient with CBD associated with mild cognitive impairment. The PET-CT study with FDG reveals severe hypometabolism throughout the right hemisphere, including the basal ganglia region and the thalamus, with the most pronounced effects in the temporo-parietal cortex (white arrow) [17].*

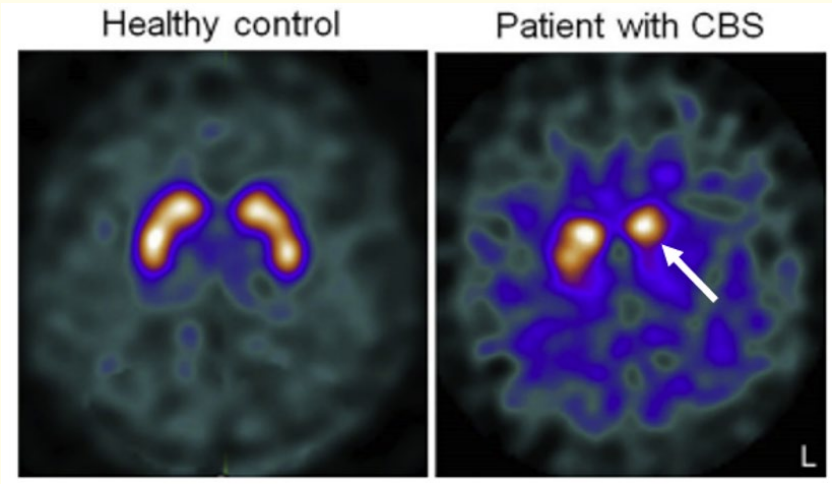

Figure 6: *DAT SPECT study of a healthy control patient (left) and a patient with CBD (right). The CBD patient shows reduced DAT uptake, bilaterally and asymmetrically in the putamen, with lower uptake in the left cerebral hemisphere (white arrow) [6].*

Diagnosis

The existence of various clinical phenotypes of CBD and the absence of pathognomonic manifestations make it challenging to arrive at a conclusive diagnosis based solely on the clinical presentation. A conclusive diagnosis is exclusively achieved through neuropathological confirmation. However, certain clinical characteristics should raise suspicion of probable or possible CBD (Table 3). The presence of any of the presentation phenotypes, insidious onset and gradual progression, onset age over 50 years, and symptom duration of at least one year are some of the diagnostic criteria. Other neurodegenerative pathologies should be ruled out through clinical examination and neuroimaging studies. The latter are not included in the diagnostic criteria, as there are no specific imaging findings for CBD [9,12].

	Probable sporadic CBD	Possible CBD
Presentation	Insidious onset and slowly progressive course	
Minimum symptom duration	1 year	
Age of onset	50 year old	No minimum
Family history (2 relatives)	Exclusion criteria	Allowed
Allowed phenotypes	Probable CBS, FBS, nfPPA with at least 1 symptom	Possible CBS, FBS, nfPPA, PSP with at least 1 symptom of CBS other than rigidity and bradykinesia.
Tau gene mutation	Exclusion criteria	Allowed

Table 3: *Clinical diagnostic criteria for CBD [22].*

Differential diagnosis

The presumptive diagnosis of CBD is clinical. It must be differentiated from other conditions with similar presentations, with the most characteristic ones being Parkinson's disease (PD) and other atypical parkinsonian syndromes. Among the etiologies associated with this syndrome are neurodegenerative diseases, infections, and/or acquired focal lesions [9] (Table 4).

Neurodegenerative diseases	• Corticobasal degeneration • Progressive supranuclear palsy • Parkinson's disease • Alzheimer's disease • Frontotemporal dementia • Dementia with Lewy bodies in motor neuron disease • Neurofilament inclusion body disease
Infections	• Jakob-Creutzfeldt disease • Progressive multifocal leukoencephalopathy
Acquired focal lesions	• Ischemic cerebrovascular disease • Karl Theodor Fahr's disease • Space-occupying mass
Miscellaneous	• Primary antiphospholipid syndrome • Spinocerebellar ataxia type 8

Table 4: *Etiologies of corticobasal syndrome (CBS).*

Progressive supranuclear palsy

PSP, like CBD, is a tauopathy that can manifest through various syndromes, many of which also serve as a presentation of CBD. The most common presentation of PSP is the Richardson-Steele-Olszewski syndrome (40%). There are some distinct features of PSP that could assist in the differential diagnosis. These include vertical supranuclear gaze palsy, typically directed downward, akinetic-rigid parkinsonism, symmetric (although in some cases it can be asymmetric) with earlier onset, and a variable response to L-dopa [2,13].

Parkinson's disease

Another diagnostic challenge is PD, which is part of the group of alpha-synucleinopathies. It is characterized by motor and non-motor disorders, with the former being the cardinal symptoms of the disease. It shares with CBD the asymmetric presentation of

rigidity, bradykinesia, postural disorders, and tremor. The main difference lies in the latter. In PD, a resting tremor is observed, with a low frequency of 4 - 6 Hz, in the form of a "coin counting" tremor, abduction and adduction of the fingers of the hand along the axis of the thumb, pronation and supination of the hands, or a combination of them. This tremor can be observed when the patient is seated, relaxed, with their hands resting on both thighs. In addition, this tremor may appear after a few seconds in the form of a postural tremor when both upper limbs are extended (re-emergent tremor). Moreover, they also share some non-motor symptoms such as depression, apathy, cognitive impairments, and executive dysfunction. PD patients may exhibit hallucinations, delusions, autonomic disturbances, sleep disorders, and sensory abnormalities, including anosmia. Finally, a diagnostic key to rule out PD and orient the diagnosis towards CBD is the lack of therapeutic response to a cycle of L-dopa [14].

Evaluation scales

Lang A, Stebbins G, Boxer A., *et al*. (2020) developed a functional evaluation scale for patients with CBD, called the "Cortical Basal Ganglia Functional Scale" (CBFS). This is a novel scale that evaluates experiences of daily living (EDL) and the degree of behavioral, language, and cognitive impairment in patients with tauopathies (4RT). The CBFS scale consists of 14 motor EVD questions and 17 non-motor EVD questions, each of which is rated according to the 5-point Likert scale from 0 to 4, where 0 = normal, 1 = insidious involvement, 2 = mild commitment, 3 = moderate commitment, and 4 = severe commitment. The questions can be answered by the patient or their caregiver. If there is a disagreement between the two, the caregiver's response should be used. Each question must be carefully analyzed, taking into account the clinical picture in the last two weeks. Questions should not be left unanswered. This scale was updated in May 2021. The estimated time to answer the questions is 25 minutes. There is currently no validated translation in Spanish [23].

Treatment

Currently, there are no treatments that can modify the biological course of DCB. Therefore, the objective of therapy is symptomatic treatment, improving the patient's quality of life. It is based on two pillars: pharmacological treatment and rehabilitation. It must be approached in a multidisciplinary manner, with the participation of different specialists, including neurologists, psychiatrists, physiatrists, occupational therapists, speech pathologists, and palliative care [1,13,19].

Treatment of motor symptoms

Parkinsonism

In general, patients with CBD do not respond to therapy with standard formulations of L-dopa. However, in up to 33% of patients, a slight improvement in akineto-rigid symptoms may be observed. Motor complications (dyskinesias) are rarely observed [30]. Due to this, in the early phase or in those cases where the presumptive diagnosis is not yet clear, this therapy can be tried. In the absence of improvement, the dose of L-dopa is gradually increased to 1000 mg/day and maintained for at least 2 months to consider the patient as a non-responder (grade B recommendation) [29]. On the other hand, dopamine agonists should be avoided due to lack of efficacy and a high rate of adverse effects. For the treatment of postural and action tremor, propranolol demonstrated good results in 20% of patients (Grade B recommendation) [1,6,13,19].

Myoclonus

The recommended drugs for the treatment of myoclonus are levetiracetam and/or clonazepam. The latter, at a dose of 2-6 mg/day, demonstrated a slight improvement in myoclonus in up to 25% of cases (Grade B recommendation) [1,6,13,19].

Dystonia

Although various drugs can improve dystonia, their multiple adverse effects limit their use since they outweigh the benefits. These are anticholinergic drugs, benzodiazepines, amantadine, and presynaptic dopamine-depleting drugs (tetrabenazine). The local application of

botulinum toxin can produce a good improvement in focal dystonia in 70% of cases, so its use is recommended (Grade B recommendation) [1,6,13,19,28].

Treatment of non-motor symptoms

Executive dysfunction and behavioral changes

There are various strategies for the management of neuropsychiatric symptoms, pharmacological and non-pharmacological. It is important to highlight to family members or caregivers the presence of depressive symptoms or behavioral changes, teach them how to detect them, and explain that they are part of the disease. The initial treatment is psychotherapy, which can be associated with different drugs. Although there are no randomized, controlled clinical trials regarding the use of antidepressants in CBD, a therapeutic trial with selective serotonin reuptake inhibitors (SSRIs) can be initiated in patients with depression, anxiety, and obsessive-compulsive disorders. Some patients may present irritability, psychosis, or develop aggressive behaviors, the management of which is usually very difficult, and atypical antipsychotics such as clozapine and/or quetiapine may be prescribed, with adequate monitoring of serum levels, given the possibility of worsening cognitive impairment or parkinsonism [6,19]. Possible hematological adverse effects of clozapine (leukopenia, anemia, thrombocytopenia) should be monitored with serial hematological studies, monthly, during the first year of treatment. In patients with apathy, the use of modafinil or methylphenidate may be considered, although there is no evidence to support this [20]. In those patients who develop cognitive impairment, the family or caregiver should be helped through occupational therapy and a change in lifestyle. This includes aerobic exercise, a proper diet, a good sleep routine, and the maintenance of social relationships [20]. The use of acetylcholinesterase inhibitor drugs (donepezil, galantamine, or rivastigmine) and memantine off-label has been described, and the possible adverse effects of the medication must be taken into account, especially with donepezil (disinhibition and compulsive behaviors) [6].

Aphasia and apraxia

The treatment of this symptomatology is mainly based on rehabilitation therapy. On the one hand, speech therapy exercises can be included to increase the pace of speech and content. Additionally, practicing other language modalities, such as signing, can help facilitate communication. On the other hand, occupational therapy can contribute to limb apraxia, either by recognizing and changing unsafe objects in the home and by simplifying daily tasks [20]. Hanna-Pladdy (2003) reports improvement in ideomotor apraxia after a stroke, as well as apraxia associated with CBD after rehabilitation therapy.

Treatment strategies

At the beginning of the disease, physical, psychological, and social support care should begin. This includes physical therapy, occupational therapy, and fall prevention programs to maintain mobility and preserve functional independence. Early intervention by physical therapy improves gait and balance. There are studies that correlate aerobic exercise with improved balance, a lower frequency of falls, and an increase in physical performance. In turn, speech therapy should be suggested to promote better communication and prevent bronchoaspirations. Nutritional support is essential to ensure adequate nutrition [6,20]. As the disease progresses, the patient's disability and dependence on the caregiver increase; therefore, another aspect to evaluate in medical check-ups is the caregiver's exhaustion and mental health [6].

Deep brain stimulation surgery

Deep brain stimulation surgery procedures have been tested in patients with DCB or CBS, using the STN (subthalamic nucleus) or GPi (globus pallidus internus) as a target, without demonstrating benefits [31].

Emerging therapies

Currently, lithium, a glycogen synthetase kinase 3-beta (GSK-3b) inhibitor, and davunetide, a neuroprotective peptide that stimulates microtubule assembly and reduces tau protein phosphorylation, have been evaluated as potential disease-modifying therapies in patients with CBD. Recently, a pilot study was conducted in patients with CBS and PSP who received lithium, which could reduce kinase activity leading to tau protein hyperphosphorylation. However, this study was stopped early because 13 of the 14 patients enrolled could not tolerate lithium. Another GSK-3B inhibitor called NP031112 (tideglusib) has been studied in patients with PSP, but the results have not yet been reported. Patients with suspected tau pathology presenting different phenotypes, including CBS, PSP, PPA nf, and fronto-temporal dementia (FTD) with parkinsonism linked to chromosome 17, recently participated in a study with intranasal davunetide, an octapeptide that interacts with microtubules and can reduce tau pathology. However, in the larger group of PSP patients, the study failed to slow disease progression compared to a group that received a placebo, so further studies with davunetide have been stopped. It is likely that the majority of therapeutic trials for CBD will continue to focus on tauopathies in general, given the difficulties in predicting the underlying pathology using clinical criteria alone and the hope of modifying the presumed tau-based pathological mechanism of the disease.

Prognosis

DCB constitutes a neurodegenerative disease that cannot be treated definitively. There are currently no therapies that modify the biological course of the disease. In two survival studies in patients with CBD, the estimated mean duration was 6.6 years (estimated range between 2 to 12 years) [24,25]. Those patients with a survival of less than one year suggest CBS due to CJD [26,27]. Patients with CBD accentuate the symptoms in a slowly progressive manner. In the course of clinical evolution, these patients may develop CBS phenotypes (CBD, FTD, PPA nf). In a prospective follow-up study of patients with CBD, predictive factors for short survival are described, namely: 1-bilateral bradykinesia, 2-frontal cortical deterioration syndrome, 3-the existence of at least two of the following extrapyramidal findings (tremor, rigidity, bradykinesia). All patients studied with CBD died of respiratory complications [29].

Conclusion

Our knowledge of CBD has increased in recent years, with advances in the field of genetics and diagnostic imaging studies. The different conditions that make up CBS and its differential diagnosis with CBD must be recognized. Various lines of research can be established regarding validation of clinical diagnostic criteria, identification of biological markers of the disease, and developing various pharmacological and non-pharmacological treatment strategies for CBD within the group of degenerative diseases characterized by the abnormal accumulation of the tau protein. The development of new treatment strategies will allow in the future to modify the biological behavior of the disease, slowing or stopping its clinical course.

Dedication

We dedicate this work to our loving families in acknowledgment of their understanding and support.

Clarification

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Gratitude

To Miss Camila Narosky Libermann, who was in charge of correcting this work.

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