Corticobasal Degeneration

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ABSTRACT

Corticobasal degeneration (CBG) is an increasingly recognized neurodegenerative disease with both motor and cognitive dysfunction. The diagnosis is probably underestimated because of the heterogeneity of clinical features, overlap with symptoms, and pathologic findings of other neurodegenerative diseases. The most characteristic initial motor symptoms are akinesia, rigidity, and apraxia. Dystonia and alien limb phenomena are frequently observed. There is often a parkinsonian picture with failure or lack of efficacy of dopaminergic medical therapy. Cognitive decline, prompting the diagnosis of dementia, may be the most common presentation of CBD that is misdiagnosed. Pathology is characterized by an asymmetric frontoparietal neuronal loss and gliosis with ballooned, achromatic cortical neurons, nigral degeneration, and variable subcortical involvement. Neuroimaging and electrophysiologic studies may help with the diagnosis but are not specific. Treatment is primarily symptomatic and minimally effective, especially after the first several years of symptoms. CBD should be considered in the differential diagnosis of patients with motor and cognitive dysfunction presenting with cortical and subcortical features. Further studies to elucidate molecular abnormalities and biological markers associated with CBD are needed to improve clinical diagnosis and treatment of patients with this disorder.

KEYWORDS: Corticobasal degeneration, atypical parkinsonism, neurodegenerative disease

Objectives: On completion of this article, the reader will be able to recognize the clinical features of corticobasal degeneration, organize an appropriate laboratory evaluation, and be able to counsel the patient and family about long-term prognosis and management.
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INITIAL DESCRIPTION

Rebeiz, Kolodny, and Richardson provided the first description of corticobasal degeneration (CBD) in 1967 and 1968.[1,2] They described three patients with slow, awkward voluntary limb movement, tremor, dystonic posturing, stiffness, lack of dexterity, and "numbness or deadness" of the affected limb. The gradual progression of symptoms included gait disorder, limb rigidity, impairment of position sense, and other sensory modalities. Cognitive function was said to remain relatively intact.

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Pathologic evaluation revealed asymmetric frontoparietal cortical atrophy and neuronal loss with associated gliosis and swelling of the neuronal cell bodies, which were devoid of Nissl substance, thus prompting them to use the descriptive term "achromatic." Pyramidal neurons in the third and fifth cortical layers were swollen with an eosinophilic and hyaline appearance with hematoxylin and eosin (H&E) staining. There was considerable loss of pigmented neurons in the substantia nigra in all three patients, variable subcortical neuronal involvement, and secondary corticospinal tract degeneration.

EPIDEMIOLOGY

CBD presents in middle to late adult life with a mean onset of symptoms at 63 years (SD ± 7.7).[3] Cases of CBD have been reported as early as 40 years old, and the youngest case with pathologic confirmation was 45 years old. Males and females are affected, and some authors have observed a predominance of women.[4–7] Current understanding suggests that it is a sporadic disease, and family histories of affected patients are usually negative. However, some have suggested that a certain genetic background may be a risk factor.[8] Other risk factors such as toxic exposures or infectious agents have not been implicated in the pathogenesis to date.

CLINICAL PRESENTATION

The clinical presentation of the motoric symptoms in CBD consists of an asymmetric parkinsonism usually of the akinetic-rigid type.[4–7] An irregular action/postural tremor is often present. The parkinsonian syndrome responds poorly to levodopa treatment. This poor response is an early and characteristic clue that suggests an atypical parkinsonian condition.[5] The symptoms are usually asymmetric upon presentation; they begin insidiously and are chronic and progressive. Riley and Lang[9] have proposed diagnostic criteria that delineate an initial presentation with a predominance of either basal ganglia or cortical signs. These criteria proposed that the clinical diagnosis of CBD be based on the presence of limb rigidity and at least one cortical sign including apraxia, cortical sensory loss, or alien limb phenomenon. An alternative CBD presentation has been proposed with rigidity, limb dystonia, and focal reflex myoclonus as the predominant features.[9]

The most common initial symptom reported is limb clumsiness with or without rigidity, and it has been observed in 50% of the patients at the first visit in some studies. Akinesia, rigidity, and apraxia[14] are the most common findings during the course of CBD, occurring in over 90% of cases within the first 3 years of illness.[9] Other less common presenting symptoms are combined arm and leg involvement, gait disorder with postural instability, speech impairment (dysphasia, dysarthria), orofacial dyspraxia, loss of facial expression, unilateral painful paresthesias, corticospinal tract signs, and behavioral problems.[4–7] It has been reported that the majority of patients with pathologic findings of CBD may have dementia as their presenting syndrome.[10]

The tremor in CBD differs from the typical rest or postural tremor seen in Parkinson's disease (PD). It is a faster (6–8 Hz) action and postural tremor, and it is more irregular and jerky.[5] Indeed, focal myoclonus may be superimposed upon the tremor during advanced stages of the disease. It is best appreciated with action, maintenance of a posture, or in response to tapping the involved limb (sensory responsive).[7] Myoclonus and tremor are seen most frequently in the most affected limb.[11]

Asymmetric limb dystonia is observed in a vast majority of patients.[3,12,13] The arm is the most frequently affected region. Usually the hand and forearm are flexed, and the arm is adducted at the shoulder. The fingers are typically flexed at the metacarpophalangeal joints, extended or flexed at the proximal and distal interphalangeal joints, and show variable degrees of fixed postures with or without associated contractures.[7,12] Head, neck, trunk, leg, foot, and toe dystonia are less common. Dystonia is often associated with rigidity, apraxia, alien limb phenomenon, and cortical sensory loss in the affected limb. As dystonia progresses, patients may develop rigid postures. Pain accompanying dystonia is described in over 40% of cases and is usually associated with contractures.[12] Choreoathetoid movements involving the limb and facial muscles may be present, usually associated with a dystonic extremity.

The alien limb phenomenon is a failure to recognize ownership of a limb in the absence of visual cues. It is associated with autonomous activity of the extremity, which may be perceived by the subject as outside his or her control. Half of patients with CBD develop the alien limb phenomenon, often with coexisting dystonia and cortical sensory loss.[14] Posturing and levitation are associated with alien limb phenomenon in CBD more commonly than in other etiologies. However, alien limb is rare on initial presentation.

Eye movement abnormalities are common in CBD and may help with early differential diagnosis. Horizontal saccadic latencies are significantly increased bilaterally in patients with CBD when compared with progressive supranuclear palsy (PSP) patients.[15] Extraocular movements are slow and hypometric with the eyes appearing to the examiner to take multiple steps to reach a target. Vertical saccades are usually normal, helping to differentiate CBD from PSP.[16] In patients with left-sided dystonia there is increased saccadic latency when pursuing to the left side only.[17] Abnormalities on electrooculography (EOG) may be evident early in the disease and may help to improve the diagnostic accuracy.[16] Blepharospasm and eyelid opening apraxia are also reported.

Cortical dysfunction in CBD patients is evident within 1 to 3 years of disease onset in most cases. Cortical signs may include apraxia, cortical sensory loss, and dementia. Ideomotor and limb kinetic apraxia can be seen in patients with CBD. Ideomotor apraxia is manifested by impairment of timing, sequencing, spatial organization, and mimicking. In limb kinetic apraxia there is a decrease in dexterity and fine movements. Ideational apraxia may be observed in later stages of the disease or in patients with dementia and language dysfunction at presentation.[18] Different types of apraxia can be appreciated depending not only on the initial affected areas but also on the pattern of disease progression. Abnormalities of two-point discrimination and somatosensory extinction to double simultaneous stimulation may be present several years before apraxia and other symptoms.[19]

CBD patients have speech changes including slowness of speech production, dysphonia, echolalia, and palilalia. The speech problems are present in the majority of patients. The difficulties may evolve to include paraphasic errors with aphasia, and patients may later become anarthric and aphonic in advanced stages. Swallowing disorders are very common, especially in advanced stages.

Cognitive and neuropsychological profiles are commonly abnormal, unlike the original description of Rebeiz et al.[1,2] Patients with clinically diagnosed CBD are similar to patients with PSP, showing difficulties particularly in executive function.[20] CBD patients, more than PSP patients, have dynamic motor execution problems and difficulties with praxis and naming. Cognition in patients with CBD also differs from that of patients diagnosed with Alzheimer's disease (AD) with extrapyramidal features. CBD patients display better performance on tests of immediate recall and attention when compared with AD patients. CBD patients show significantly worse performance on tests of praxis, digit span, and unimanual and bimanual motor series examinations. Recognition memory may be preserved but encoding and recall strategies are dysfunctional. A frontosubcortical pattern of dementia associated with gesture disorders is considered as very suggestive of CBD.[21]

Neuropsychological features include depression in 73%, apathy in 40%, irritability in 20%, and agitation in 20% of patients diagnosed with CBD.[22] Less common but also reported are anxiety, disinhibition, delusions, or aberrant motor behavior. Left-sided symptoms as a result of right hemisphere involvement include increased disinhibition, apathy, and irritability. Further, they have lower depression scores than patients with predominant left hemisphere involvement. Obsessive-compulsive disorder (OCD) manifestations, including recurrent thoughts, repetitive acts, indecisiveness, checking behaviors, and preoccupation with perfectionism, are also included in the neuropsychological profile (Table 1).[22]

Table 1 Clinical Features of CBD

Nature of symptoms
Insidious, chronic, progressive
Asymmetric onset
Unresponsive to levodopa
Motor dysfunction
Limb clumsiness, bradykinesia, akinesia, rigidity
Action/postural tremor
Myoclonus (focal, multifocal)
Limb dystonia (asymmetric early)
Blepharospasm
Orolingual dyskinesias
Choreoathetoid movements
Speech problems (monotonous dysarthria, anarthria late)
Gait disorder, postural instability, falls
Supranuclear gaze abnormalities (voluntary saccades affected more than smooth pursuit)
Upper motor neuron syndrome/corticospinal signs
Higher cortical dysfunction
Limb apraxia (ideomotor, limb kinetic, ideational, or constructive)
Orofacial apraxia
Eyelid opening apraxia
Cortical sensory abnormalities (extinction to double simultaneous somatosensory stimulation, agraphesthesia, astereognosis)
Alien limb phenomenon
Aphasia
Frontal lobe release signs
Dementia
Neuropsychiatric abnormalities:
Depression
Apathy
Anxiety
Irritability
Agitation
Disinhibition
Delusions
Obsessive compulsive disorder (OCD)

PROGNOSIS

Symptoms associated with shorter survival in CBD patients are early onset of bilateral parkinsonism and the presence of a frontal lobe syndrome. The symptoms are progressive and death usually ensues 5 to 10 years (7.9 ± 2.6)[3] after disease onset.

LABORATORY STUDIES

Routine laboratory studies of blood, urine, and cerebrospinal fluid are normal. Serum copper and ceruloplasmin levels are normal. Heavy metal toxic screens of urine are normal. Somatostatin levels in cerebrospinal fluid are significantly decreased in some patients.[23]

RADIOGRAPHIC STUDIES

Brain computed tomography (CT) and magnetic resonance imaging (MRI) are usually normal in early stages of the disease. As the disease progresses, a pattern of asymmetric posterior frontal and parietal cortical atrophy becomes evident with dilatation of the lateral ventricle. In intermediate to advanced stages, a pattern of bilateral cortical atrophy may be seen. The asymmetric focal atrophy is observed in a majority of patients. Imaging abnormalities of the basal ganglia are generally absent. As the cortical atrophy becomes more prominent, abnormal signal attenuation is seen in the underlying subcortical white matter. Abnormalities of the cortex are more easily detectable with fluid attenuated inversion recovery (FLAIR) sequences in the MRI.[24] Atrophy and abnormal signal in the corpus callosum are characteristic as a result of the cortical degeneration. The degree of cognitive impairment shows a strong correlation with the severity of callosal atrophy and ventricular dilatation.[25] Serial evaluations of CT or MRI scans over time at 6- to 12-month intervals are generally more useful than analysis of isolated scans.

MRI can provide strong support for the diagnosis and may be helpful in distinguishing CBD from other neurodegenerative disorders.[26] The radiologist must be aware of the importance of observing cortical asymmetries when evaluating brain images of patients with suspected CBD. Compared with CBD, MRI in patients with PSP shows atrophy in the midbrain. AD may be differentiated from CBD by recognizing diffuse temporal and hippocampal atrophy in AD. MRI in patients with striatonigral degeneration (SND) demonstrates T2 hypointensities in the posterior lateral putamen, and the atrophy in multisystem atrophy (MSA) of the olivopontocerebellar atrophy (OPCA) type is more evident in the pons and cerebellum.[26]

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used in CBD to study changes in cerebral blood flow (CBF), cerebral metabolism (oxygen or glucose), and nigrostriatal dopaminergic function. CBD patients show a global reduction of oxygen and glucose metabolism (fluorodeoxyglucose, FDG) most prominent in the cerebral hemisphere contralateral to the most affected limb.[27] There is a corresponding reduction of CBF most evident in the frontoparietal, medial frontal, and temporal cortical regions.[28–30] The only significantly affected subcortical area is the thalamus, where metabolism can be asymmetrically reduced by 15%.[27] Dysfunction of the nigrostriatal dopaminergic system has been demonstrated by decreased ^{18}fluorodopa (F-dopa) uptake in the striatum with PET and reduced postsynaptic striatal D2 receptor binding of [^{123m}I]-iodobenzamide (IBZM) on SPECT scanning. SPECT labeling of the dopamine transporter by 2β-carboxymethoxy 3β(4-odophenyl)-tropane [^{123}I]β-CIT has demonstrated symmetrical striatal reduction in clinically diagnosed CBD, PSP, and MSA compared with an asymmetric reduction in PD. Striatal F-dopa uptake can be reduced in CBD patients to as low as 25% of normal values.[30] Caudate and putamen are similarly affected in CBD, whereas in PD patients F-dopa uptake is selectively reduced in the putamen.[26–30] The combination of both cerebral glucose utilization and F-dopa metabolism in the nigrostriatal system can provide information about the pattern of dysfunction and help to corroborate a clinical suspicion of CBD.

The characteristic pattern of asymmetrically reduced frontoparietal cerebral cortical metabolism and/or CBF coupled with bilateral reduction of F-dopa uptake in the caudate and putamen provides strong supportive evidence in a patient with a clinical diagnosis of possible CBD.[31]

ELECTROPHYSIOLOGICAL STUDIES

The electroencephalogram (EEG) is usually normal on initial presentation of symptoms. As the disease progresses, the EEG may reveal asymmetric slowing, most prominent over the cerebral hemisphere contralateral to the most affected limb.[5,7] Spike discharges are not usually present. In later stages, the EEG may show nonspecific bilateral slowing. Electrophysiologic studies of the myoclonus seen in CBD patients demonstrate that it is a reflex myoclonus and there is absence of preceding cortical discharge. The myoclonus is best recorded using provocative maneuvers such as intentional movements of the limb, startle, or tactile stimulation of the affected limb(s). Pathophysiologically, reflex myoclonus in CBD may be caused by enhancement of the response to direct sensory input or by exaggeration of inputs in motor cortical areas due to increased cortical excitability.[11]

Somatosensory evoked potentials (SSEPs) are of minimal utility in evaluating patients with suspected CBD. Thalamocortical potentials of the SSEPs are occasionally prolonged.[32,33] Brain stem auditory EPs are also usually normal, but significant prolongation of the N200 and P300 latencies may be found occasionally in patients with both CBD and PSP.[33,34] Visual evoked potentials are normal in almost all cases but prolonged P100 latencies can be seen rarely. Routine electromyography and nerve conduction studies show occasional focal or generalized neuropathies that are usually subclinical.

NEUROPATHOLOGY

Gross Findings

Superior frontoparietal cortical atrophy in CBD is often asymmetrical and involves perirolandic cortex.[6] The cortical atrophy may also affect more rostral, middle, and inferior frontal cortical gyri. Cingulate and insular

cortex may show variable involvement but temporal cortex is usually unaffected unless concomitant AD pathology is present.[35] Occipital and cerebellar cortices are spared. Involvement of subcortical nuclei varies widely from case to case in both severity and topography. Transverse sections of the brain stem show severe loss of neuromelanin pigment in the substantia nigra; however, neuromelanin of the locus ceruleus is preserved. The head of the caudate may have a flattened appearance, and the thalamus in CBD cases tends to be smaller than normal. The cerebral white matter adjacent to affected areas is often attenuated. The cerebral peduncles may show attenuation and degeneration of corticobulbar and corticospinal fibers. Prominent atrophy of the pons, medulla, and dentate nucleus suggests an alternative diagnosis such as MSA. In addition, there may be hydrocephalus ex vacuo, dilatation of the aqueduct of Sylvius, and atrophy of the corpus callosum,[25] all resulting from neuronal loss and reduction of the associated neuropil.

Microscopic and Ultrastructural Findings

Microscopic examination reveals neuronal loss and gliosis in cortical and subcortical regions. Superficial spongiosis in atrophic cortical regions is common. In CBD there is an astrocytic gliosis more marked in the superficial layers of the cortex and at the gray-white junction. Basal ganglia, thalamus, periaqueductal gray matter, red nucleus, subthalamic nucleus, dentate nucleus, and inferior olivary nucleus may all exhibit a variable degree of involvement.[6,7] The substantia nigra displays a moderate to marked neuronal loss with extraneuronal neuromelanin visualized within phagocytes.[7] In the white matter there is loss of axons and myelin in regions underlying involved cortex with gliosis along the corticostriatal and the corticobulbar fibers.

Ballooned and achromatic neurons are a characteristic feature of CBD.[2,7,35,36] They are most commonly seen in deep layers of degenerated frontoparietal cortex but may be observed in other cortical and subcortical regions including anterior cingulate gyrus, amygdala, insular cortex, and claustrum. Ballooned neurons lack Nissl substance, are eosinophilic on H&E staining, and are often vacuolar. Ballooned neurons do not stain positive for α-synuclein using immunocytochemistry, a sensitive and specific marker for cortical Lewy bodies. They are sometimes positive for ubiquitin immunocytochemical staining but not for epitopes specific to AD. Ballooned neurons are also found in Pick's disease, PSP, AD, Creutzfeldt-Jakob disease (CJD), and amyotrophic lateral sclerosis (ALS).[36,39,41] There is substantial neuropathological overlap between Pick's disease, PSP, and CBD.[35,37,38] The three disorders may have ballooned neurons, variable degeneration of the substantia nigra, variable degeneration of basal ganglia, and tau-positive inclusions.[6,39] Pick bodies, a characteristic feature of Pick's disease, are rarely observed in CBD. Although CBD and Pick's disease exhibit asymmetrical cortical atrophy, the temporal cortex and the hippocampus are usually involved in Pick's disease but spared in CBD. The subcortical pathology in CBD and PSP has multiple similarities, explaining the high frequency of CBD cases being misdiagnosed clinically as PSP.[6,13,16]

Tau-Associated Changes

Tau is a microtubule-associated phosphoprotein that promotes tubulin polymerization and stabilization of microtubules.[39] Tau is present mainly in axons and expressed also in glial cells, especially in pathologic conditions. The current evidence indicates that tau protein in CBD is generated from transcripts of exon 10 on chromosome 17.[8] The tau protein undergoes extensive phosphorylation which controls its functional state. In the normal state tau is unfolded, soluble, and heat stable. Pathological tau has abnormal phosphorylation and solubility and forms abnormal filamentous structures. Phosphorylated tau is less efficient in promoting tubulin polymerization. Focal tau immunoreactivity is detected in ballooned neurons, neurofibrillary tangles, neuropil threads, grains, glia, and neuronal inclusions.[37,40] They are frequently identified on silver stain preparations and on tau immunohistochemistry within cortical neurons, underlying white matter, globus pallidus, caudate, putamen, subthalamic nucleus, red nucleus, and brain stem nuclei. The locus ceruleus, raphe nuclei, tegmental gray matter, and substantia nigra have frequent neurofibrillary lesions that are tau immunoreactive.[40]

Tau pathology in glial cells is also expressed in CBD.[37] The most characteristic tau-immunoreactive astrocytic lesion in CBD is a grain-like process that resembles the neuritic plaque of AD. Tau-positive astrocytic plaques are argyrophilic structures identified in many cases of CBD. They are thought to be characteristic of CBD although they have also been observed in PSP.[40] The plaques in CBD do not contain amyloid and are glial in origin.[40] The tau-positive glial inclusions of CBD are different from the glial inclusions of MSA, which are immunoreactive for ubiquitin and α-synuclein but negative for tau (Table 2).[42]

Genetic and Molecular Findings

It is suggested by some authors that CBD and PSP could be different clinical manifestations of the same pathological entity, based on the overrepresentation of the same haplotype of the tau protein gene located in chromosome 17. Further work is needed in this area to fully confirm or refute this claim.[8]

Apolipoprotein E e4 allele, which carries an increased risk of AD, is increased in CBD as well as in Pick's disease and PSP.[6]

Table 2 Neuropathological Features of CBD

Gross findings
Superior frontoparietal and perirolandic cerebral cortical atrophy—asymmetric
Enlargement of lateral ventricles—asymmetric
Reduction of cerebral white matter, internal capsules, and cerebral peduncles—asymmetric
Thinning of corpus callosum
Pallor of substantia nigra
Microscopic findings
Neuronal loss, gliosis and swollen, ballooned achromatic neurons in cerebral cortex—especially frontoparietal
Disorganization of laminar pattern of cerebral cortex in regions of heavy neuronal loss
Abnormal cerebral white matter—swollen axons, demyelination of axons, spongiform appearance of neuropil in regions of heavy neuronal loss
Pigmented neuron loss and gliosis in substantia nigra
Variable neuronal loss and gliosis in subthalamic nucleus, globus pallidus, corpus striatum, red nucleus, claustrum, thalamus, dentate and cerebellar roof nuclei, and scattered brain stem nuclei
Immunocytochemical findings
Positive immunoreactivity of swollen, achromatic cortical neurons and axons with antibodies to phosphorylated neurofilaments
Positive immunoreactivity of subcortical and cortical neurons with antibodies to tau (corticobasal bodies; globose neurofibrillary tangles)
Positive immunoreactivity of clusters of astrocytic processes in cortex with antibodies to tau (astrocytic plaques)
Negative immunoreactivity of swollen, achromatic neurons with antibodies to α-synuclein

DIAGNOSIS

Clinicians and neuropathologists are increasingly aware of the overlap and heterogeneity among neurodegenerative diseases. When taken alone, the clinical symptoms, neuropathological findings, laboratory studies, and neuroimaging or electrodiagnostic tests are not specific enough to allow the diagnosis of CBD. Currently the diagnosis is best made based on the combination of characteristic clinical features, supportive data from ancillary studies, and postmortem pathological examination. CBD is currently underdiagnosed by most clinicians, given the heterogeneity in clinical expression and pathological findings.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis must include the neurologic disorders that can share symptoms with CBD.[7] The pattern of common motoric deficits in CBD is sufficiently distinctive that when present it should not be mistaken for PD. However, this is the most common misdiagnosis early in the course of the disease when the patients may show only "extrapyramidal" motor symptoms. The best early clues that help differentiate CBD from PD are the lack of a beneficial response to levodopa and the emergence of cortical signs such as apraxia or abnormal cortical sensation. Disorders that present as atypical parkinsonism, most notably PSP,[41] striatonigral degeneration,[43,44] MSA[44–46] (including olivopontocerebellar atrophy), atypical variants of Pick disease,[47–50] AD with extrapyramidal features,[51,52] and the parkinsonism-dementia-ALS complex,[52,53] must be considered in the differential diagnosis. PSP is the one most likely to be confused with the motoric presentation of CBD. PSP classically presents with prominent axial rigidity, postural instability with frequent early falls, and abnormal vertical eye movement. Atypical manifestations of PSP such as asymmetric onset, mild oculomotor impairment, focal dystonia, and involuntary limb levitation resembling the alien limb phenomenon are the most frequent features that may cause confusion with CBD.

Asymmetric cortical degenerations including primary progressive aphasia (PPA), Pick's disease, and AD may present with features resembling early CBD such as focal myoclonus, apraxia, alien limb phenomenon, and asymmetric rigidity.[51] These syndromes, in general, lack the prominent and progressive extrapyramidal dysfunction characteristic of the typical motor presentation of CBD. However, it is now clear that CBD frequently presents with dementia[10] and therefore it is important to include it in the differential diagnosis of primary dementing disorders. If a patient presents with a "rapidly progressive" CBD-like picture, prion-related disease should be considered (Table 3).[54]

THERAPY

Pharmacotherapy for CBD has generally been of limited benefit. The treatment efforts are focused on alleviating rigidity, dystonia, tremor, myoclonus, neuropsychological symptoms, and other manifestations. Part of the difficulty in designing effective pharmacotherapy for CBD is the widespread pathological involvement of

Table 3 Differential Clinical Diagnostic Features in Patients with Overlap of Motor and Cognitive Dysfunction

Diagnosis	Principal Clinical Features	Features Suggesting Another Disorder or Concurrent Pathology
CBD	Apraxia, cortical sensory loss, unilateral or asymmetric rigidity and dystonia, action tremor superseded by focal myoclonus, alien limb behavior, rapid course, lack of response to L-dopa therapy	Prominent ocular impairment, axial rigidity or dystonia out of proportion to limb involvement, rest tremor, autonomic failure, aphasia
PSP	Supranuclear ophthalmoplegia (especially vertical), axial dystonia in extension, early gait impairment and postural instability, dysarthria and pseudobulbar palsy, frontal lobe–type dementia (dysexecutive syndrome), lack of or suboptimal response to L-dopa therapy	Lack of or minimal ocular impairment, asymmetric rigidity, prominent dementia early in course, alien limb–type behavior, apraxia, cortical sensory loss
MSA	Symmetric rigidity (less commonly asymmetric), lack of rest tremor, cerebellar and autonomic dysfunction, choreoathetosis, rapid course, lack of or suboptimal response to L-dopa therapy	Early and prominent ocular impairment, apraxia, cortical sensory loss
PD with dementia	Rest tremor, bradykinesia, asymmetric rigidity, gait impairment, memory loss, dementia, L-dopa responsiveness	Symmetric rigidity, lack of rest tremor, axial dystonia, early ocular impairment, early myoclonus, apraxia, cortical sensory loss, lack of or suboptimal response to L-dopa therapy
DLBD	Early cognitive dysfunction (especially with fluctuating features), L-dopa–induced psychosis, mild parkinsonism (initially)	Isolated cortical dysfunction (memory loss, aphasia, apraxia, cortical sensory loss, frontal lobe dementia), axial rigidity and dystonia, ophthalmoplegia
AD with extrapyramidal dysfunction	Early cognitive impairment (especially memory loss), cortical dysfunction (visuospatial, language, praxis), mild bradykinesia and rigidity, protracted progressive course	Parkinsonism before memory loss, progressive frontal lobe dysfunction, aphasia or apraxia without significant memory loss, early gait impairment, axial rigidity, ophthalmoplegia, alien limb–type behavior
Pick's disease	Prominent frontal lobe dementia with personality changes (disinhibition or apathy, aphasia, memory loss)	Progressive aphasia or apraxia without dementia, prominent extrapyramidal features, rest tremor, L-dopa responsiveness, ophthalmoplegia
CJD	Rapid course of dementia, personality changes, myoclonus; upper motor neuron, cerebellar and/or extrapyramidal signs	Protracted course isolated parkinsonism or cortical dysfunction (apraxia, cortical sensory loss), rest tremor, L-dopa responsiveness

CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; PD, Parkinson's disease; DLBD, diffuse Lewy body disease; AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease.
Adapted from Watts et al.[7]

different subcortical and cortical neuronal systems and the lack of knowledge of the full biochemical and molecular background to explain the pathophysiology of the various manifestations.

Therapy of Motor Dysfunction

CBD patients show modest to no beneficial response to carbidopa/levodopa and other dopaminergic agents. Improvement in clinically diagnosed CBD occurred in 24% of patients receiving carbidopa/levodopa in one report.[55] The rest of the dopaminergic agents (bromocriptine, pergolide, pramipexole, ropinirole, selegiline) provide less clinical improvement and produce more side effects. Clonazepam has been the most beneficial agent for treatment of the action tremor and myoclonus, but lorazepam, diazepam, and alprazolam have also been used with some benefit.

Baclofen and tizanidine may improve rigidity and tremor, but they have only a modest effect. Anticholinergics have been reported to yield benefit in a small number of patients but their benefit wanes quickly and they are poorly tolerated.[55] Likewise, amantadine is of little or no benefit and may produce side effects. Botulinum toxin injections may be useful in the treatment of painful focal upper limb dystonia and blepharospasm.[12]

Stereotactic thalamotomy and pallidotomy for relief of severe painful limb dystonia and parkinsonian symptoms have been of little or no benefit, and thus they are not indicated in the treatment of this disorder.[56]

Therapy of Neuropsychiatric Features

Small doses of atypical neuroleptic medications such as quetiapine, olanzapine, or clozapine may be helpful if paranoid delusions, psychotic behavior, agitation, irritability, and sleep problems emerge. The use of typical antipsychotic medications such as haloperidol may worsen CBD motor symptoms and they are not recommended.

Depression and obsessive-compulsive symptomatology may be treated effectively with selective serotonin reuptake inhibitors (SSRIs), but caution and low doses are recommended because these medications can exacerbate agitation.[22] Antidepressants with anticholinergic side effects, including tricyclic compounds, may exacerbate confusion.[55]

Small doses of sedative hypnotic agents may be helpful for sleep problems, but they also may exacerbate confusion and agitation. Clonazepam is usually helpful, and agents such as diphenhydramine, chloral hydrate, and zolpidem may be useful. Small doses of an atypical antipsychotic, as mentioned before, decrease sleep onset latency and increase overall sleep time.

Treatment of Other Symptoms

Gastrointestinal symptoms in CBD patients include hypersalivation, dysphagia, nausea, and constipation. Excessive salivation may respond to small doses of anticholinergic therapy but side effects are limiting in most cases.

The goal of treatment of the dysphagia is to maintain safe and efficient nutrition and hydration. Evaluation with a barium swallow study may be necessary. Treatment includes dietary modifications, postural changes, swallowing maneuvers and exercises, and surgical interventions. Selection of foods with a consistency that facilitates swallowing is a critical aspect. Some patients may require thickened liquids. If they are not able to ingest enough food to meet nutritional requirements, a percutaneous feeding gastrostomy tube placement may be necessary. The decision to place a gastrostomy in a patient with a chronically progressive neurodegenerative disease must be handled on an individual basis.

Constipation in parkinsonism is due to colonic hypomotility, outlet dysfunction, or both. Constipation has also been associated with pelvic floor dystonia. The use of stool softeners, increased fluid intake, food rich in fiber, and laxatives may be beneficial. Polyethylene glycol is another alternative for the treatment of severe constipation. The urinary symptoms in CBD patients include urgency and frequency, and they may improve with the use of hyoscyamine, tolterodine, or oxybutynin. Close observation for central and peripheral side effects is warranted when using these or related medications. Symptomatic orthostatic hypotension, although more frequently seen in MSA, may be treated with fludrocortisone or midodrine.

Other aspects of patient care, not involving pharmacotherapy, can be of special importance for these patients and their families. Physiotherapy is very helpful for maintenance of mobility and prevention of contractures. Pain related to dystonic posturing can be lessened by maintenance of good range of motion, and occasionally splinting can be helpful. Occupational therapy can help patients maintain some degree of functional independence by providing specially made devices such as eating utensils with large handles. Speech therapy may offer practical suggestions and exercises to optimize speech function and guard against aspiration secondary to swallowing difficulty. Good home care assistance can help prolong the time a patient can remain at home before requiring nursing home placement.

Despite all our best therapeutic efforts, the disease generally progresses to a state of bilateral rigid immobility, and the patients usually die from aspiration pneumonia or urosepsis.

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