Corticobasal syndrome

Five new things

Lama M. Chahine, MD

Tanya Rebeiz, MD

Jean J. Rebeiz, MD

Murray Grossman, MD, EdD

Rachel G. Gross, MD

Summary

Corticobasal syndrome (CBS) is characterized by asymmetric involuntary movements including rigidity, tremor, dystonia, and myoclonus, and often associated with apraxia, cortical sensory deficits, and alien limb phenomena. Additionally, there are various nonmotor (cognitive and language) deficits. CBS is associated with several distinct histopathologies, including corticobasal degeneration, other forms of tau-related frontotemporal lobar degeneration such as progressive supranuclear palsy, and Alzheimer disease. Accurate antemortem diagnosis of underlying pathology in CBS is challenging, though certain clinical and imaging findings may be helpful. Five recent advances in the understanding of CBS are reviewed, including clinical and pathologic features, imaging and CSF biomarkers, the role of specific genes, and the concept of a spectrum of tauopathies.

In 1967 and 1968, Rebeiz et al.^{1,2} reported clinicopathologic findings of 3 patients with a previously undescribed syndrome they named corticodentatonigral degeneration with neuronal achromasia. Over ensuing years, several reports emerged, culminating in the present-day body of knowledge that reveals a fascinating, yet challenging, diagnostic conundrum. Indeed, it has become clear that the clinical features described by Rebeiz et al. are associated with various pathologies and conversely, that the pathology first described by Rebeiz et al. can be seen in patients with a wide array of neurologic signs and symptoms. This clinical-pathologic diversity has motivated adoption of 2 distinct terms: corticobasal degeneration (CBD), in which pathologic findings described by Rebeiz et al. are present, and corticobasal syndrome (CBS), which refers to the clinical phenotype independent of underlying histopathology. Thus, in this article, reference to CBS implies no assumptions regarding the underlying pathology, and when reference to specific pathologies such as CBD is made, evidence from the literature is drawn from studies in which pathologic confirmation of the diagnosis was available.

Department of Neurology (LMC, MG, RGG), University of Pennsylvania, Philadelphia; Department of Neurology (TR), University of Chicago, IL; and Department of Internal Medicine and Pathology (JJR), American University of Beirut, Lebanon.

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Correspondence to: lamachahine@hotmail.com

Table 1 Clinical features described in corticobasal syndrome⁵⁻¹⁰

Parkinsonism (rigidity, bradykinesia, tremor, and postural instability)
Limb apraxia
Alien limb phenomena
Dystonia
Kinetic and rest tremor
Myoclonus
Cortical sensory loss
Apraxia of speech
Dysequilibrium
Cerebellar findings
Blepharospasm
Upper motor neuron findings (hyperreflexia, Babinski sign)
Dysarthria
Unilateral periodic limb movements during sleep
Orolingual dyskinesia
Athetosis

Therapeutics in neurodegenerative diseases are increasingly targeting the underlying pathologic process.³ Thus, it is essential to distinguish between the various types of neurodegenerative disorders, with accurate antemortem diagnosis and definition of diagnostic criteria assuming increasing importance. Given the etiologic heterogeneity of CBS, characterization of this disorder has been the focus of substantial effort, and important new data and concepts have emerged in regard to it in recent years. This review discusses 5 new aspects of CBS: clinical features, pathologic features, biomarkers, the role of specific genes, and the concept of a tauopathy spectrum.

Clinical features of CBS

Motor features CBS is considered to be an atypical parkinsonian syndrome. Prominent features include marked asymmetry in motor abnormalities, including dystonia, rigidity, myoclonus, and tremor, as well as a “useless arm” with or without alien limb phenomena. While myoclonus was not reported in the original description, others have considered reflex, stimulus-sensitive myoclonus to be suggestive of CBS.⁴ Several other motor manifestations have been reported (table 1).

In a recently proposed diagnostic classification scheme,⁵ core motor features of probable CBS include (1) an asymmetric presentation including ≥ 2 of the following: limb rigidity/akinesia, dystonia, or myoclonus, as well as (2) ≥ 2 of the following features: orobuccofacial or limb apraxia, cortical sensory deficit, or alien limb phenomena.⁵ Further criteria based on associated motor, cognitive, and language deficits were included.⁵

Some motor features may help predict underlying pathology in cases of CBS. For example, while a subset of CBS patients (with various underlying pathologies) transiently respond to levodopa and may even have dyskinesias,⁷ a sustained response to levodopa (for over 2 years) suggests, in the right clinical context, a diagnosis of idiopathic Parkinson disease. While there are no eye movement abnormalities that reliably distinguish underlying pathology in CBS, reduced velocity of vertical saccades is most consistent with progressive supranuclear palsy (PSP).¹¹ Overall, however, it is increasingly recognized that motor features do not reliably distinguish between CBS cases with various underlying pathologies.^{5,8,9} For example, cortical

Table 2 Diagnoses reported in patients with corticobasal syndrome (pathologically proven or diagnosed based on laboratory or genetic testing)

Corticobasal degeneration ^{1,2}
Alzheimer disease ^{16,17}
Pick disease ^{12,17}
Progressive supranuclear palsy ¹⁷
Dementia with Lewy bodies (Gross et al., personal communication, 2013)
Nonspecific degenerative changes ^{12,17}
Neurofilament inclusion body disease ¹⁸
MAPT gene mutation (frontotemporal dementia and parkinsonism linked to chromosome 17)
Frontotemporal lobar degeneration-TDP43 with motor neuron disease ^{7,8}
Progranulin gene mutation (frontotemporal dementia linked with ubiquitin inclusions on pathology) ^{19,20}
Progressive multifocal leukoencephalopathy ^{e1}
Cerebrovascular disease ¹⁶
Creutzfeldt-Jakob disease ¹⁷
Fahr disease ^{e2}
Neurosyphilis ^{e3}
Spinocerebellar ataxia type 8 ^{e4}
Central pontine myelinolysis ^{e5}
Microtubule-associated protein tau (MAPT) gene mutation ^{e6}
Leucine-rich repeat kinase 2 (LRRK2) gene mutation ^{e7}
Cerebrotendinous xanthomatosis ^{e8}
Carotid artery stenosis/occlusion ^{e9,e10}
C9orf72 hexanucleotide expansion ^{e11}

sensory loss and myoclonus, classically considered key features of CBD, have in fact been shown to be associated with either CBD or Alzheimer disease (AD) pathology.^{7,10}

While the motor syndrome of CBS is distinct from other neurodegenerative parkinsonian syndromes, there are few specific motor features that reliably predict underlying pathology.

Cognitive features Rebeiz et al.¹ specifically noted absence of cognitive involvement in early stages of the disease, but it is now clear that cognitive and language disturbances are prominent in CBS, even in those cases that are secondary to underlying CBD pathology. Among patients with neurodegenerative disorders who manifest features of CBS in the course of their disease, motor features of CBS are the presenting signs and symptoms in some cases, with language or cognitive syndromes, or both, subsequently developing. However, in other patients, the reverse occurs^{9,12–14}; specific focal dementia syndromes such as behavioral-variant frontotemporal dementia (FTD), primary progressive aphasia including progressive nonfluent aphasia, and posterior cortical atrophy^{8,9} could be the presenting and most prominent features, with motor features of CBS then emerging later, as a secondary or tertiary syndrome.¹³

Like motor features, there are no cognitive or language manifestations that reliably distinguish between underlying pathologies in patients with CBS. One study suggested that episodic memory complaints may predict AD pathology in patients with CBS, and evidence for frontal lobe dysfunction (such as nonfluent language deficits and utilization behavior) may predict CBD.¹⁰ However, others have not demonstrated distinct cognitive profiles in CBS cases with underlying AD vs CBD pathology.¹⁵

Table 3 Distinguishing neuropathologic features of the most common forms of frontotemporal lobar degeneration that may present as corticobasal syndrome

Disorder	Distinguishing microscopic features among tauopathies	Notes
Corticobasal degeneration	Swollen, "achromatic" "ballooned" neurons scattered in third, fifth, and sixth cortical layers in affected cortical regions	Ballooned neurons in cortical convexity areas are specific for CBD ^{e14} (contrast to distribution in argyrophilic grain disease below)
	Tau-positive astrocytic plaques in affected neocortex and subcortical white matter and in the basal ganglia ^{e14,e15}	"Coiled bodies" are tau-positive and α -synuclein-negative whereas the "glial cytoplasmic inclusions" typical of multiple system atrophy are immunoreactive for ubiquitin and α -synuclein, but usually negative for phosphorylated tau ^{e14}
	Tau-positive argyrophilic inclusions in oligodendroglia, "coiled bodies" ^{e14}	"Coiled bodies" are seen in both PSP and CBD but are generally at a lower density than inclusions in astrocytes ^{e15}
	Tau-positive thread-like lesions in neocortex, basal ganglia, and brainstem nuclei ^{e15}	Greater corpus callosum atrophy may be seen in CBD compared to PSP ^{e16}
		The distinction between CBD and another tauopathy that can present as CBS, frontotemporal degeneration with parkinsonism-17 (FTDP-17, also called FTD with microtubule-associated tau [MAPT] gene mutation) cannot be made on a neuropathologic basis but rather only when taking clinical features, family history, and molecular genetic information into account ^{e14}
Progressive supranuclear palsy	Most characteristic neuronal lesion is the globose neurofibrillary tangle	Tufted astrocytes, abundant in perirhinal cortices and striatum, are characteristic of PSP and morphologically distinct from astrocytic plaques of CBD ^{e14}
	Neurofibrillary tangles in subcortical regions including basal ganglia, subthalamic nucleus, midbrain, and pontine nuclei ^{e15}	Neuronal loss and atrophy of subthalamic nucleus is usually marked in PSP and minimal in CBD ^{e14}
	Glial lesion: tau-positive "tufted" astrocytes in affected neocortical and subcortical regions (basal ganglia, subthalamic nucleus, and the substantia nigra; cortical involvement greatest in motor and premotor cortices; cerebellar dentate nucleus and dentato-rubro-thalamic pathway severely affected with atrophy of superior cerebellar peduncle) ^{e14,e15}	
FTLD with Pick bodies	Pick bodies (argyrophilic, round, tau-positive neuronal cytoplasmic inclusions) in nonpyramidal (dentate gyrus granule cells) and pyramidal neurons of area CA1 of the hippocampus, and pyramidal neurons of the temporal and frontal lobes ^{e15}	A useful means of differentiating CBD and Pick disease is with the Gallyas stain; unlike CBD, lesions in Pick disease are negative with the Gallyas stain ^{e14,e15}
		Tau in Pick bodies is the 3R isoform; the tau-positive inclusions of PSP and CBD are 4R ^{e14,e15}
Argyrophilic grain disease	Tau-positive ovoid structures (glial processes), tau-positive astrocytes	Ballooned neurons in cingulate gyrus, amygdala, insular cortex, and claustrum occur in argyrophilic grain disease as well as CBD but their presence in the cortical convexity suggests CBD ^{e14}
	Oligodendroglial "coiled bodies" confined to the medial temporal lobe and limbic structures ^{e15}	

Abbreviations: CBD = corticobasal degeneration; FTLD = frontotemporal lobar degeneration; PSP = progressive supranuclear palsy.

Supplemental Data

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Like motor features, there are no cognitive or language manifestations that reliably distinguish between underlying pathologies in patients with CBS.

Clinicopathologic correlates of CBS

A multitude of etiologies have been reported in patients with CBS (table 2). As mentioned above, predicting underlying pathology in CBS is difficult,^{14,e12} particularly in the first 3 years of symptoms. For example, the sensitivity of clinical findings for predicting underlying CBD pathology ranges from 26.3% to 56.0%.^{7–9,e13} While some series have suggested that dementia syndromes (FTD or AD) are the most common misdiagnoses in cases of CBD,^{8,9} in others, CBD was most often misdiagnosed as PSP during life.⁷ Retrospective case series are frequently confounded by a referral bias that influences relative proportions of the various clinical presentations.

While distinguishing between etiologies of CBS is clinically challenging, neuropathologic diagnosis of the most common neurodegenerative causes of CBS is facilitated by specific findings in each case. As elaborated on further below, the majority of causes of CBS are tauopathies, and emergence of tau staining over the past decade has dramatically enhanced immunohistochemical characterization of these disorders (table 3). Tau exists in various isoforms, and each of the neurodegenerative disorders that can cause CBS have been associated with specific tau isoforms. CBD and PSP are associated with a tau isoform with 4 microtubule-binding repeats (4R tau) in neuronal and glial structures.^{e17} By comparison, other tauopathies such as dementia with Pick bodies are associated with 3 microtubule-binding repeats (3R). In AD, tau tangles consist of both 3R and 4R isoforms of tau. This may ultimately have therapeutic implications if isoform-specific tau therapies are developed.

In addition to immunohistochemical features that distinguish the different pathologic causes of CBS, distinct microscopic findings also characterize the neurodegenerative causes. For example, in CBD, achromatic “ballooned” neurons are present in the cortex, cingulate gyrus, amygdala, insula, and claustrum (table 3). The presence of thread-like tau-positive neuronal and glial lesions and astrocytic plaques is also considered highly suggestive of CBD. Astrocytic plaques distinguish CBD from PSP, in which tufted astrocytes are present. “Coiled bodies,” or oligodendroglial tau-positive argyrophilic inclusions, are common in CBD, and are distinct from the tau-negative oligodendroglial lesions (glial cytoplasmic inclusions) of multiple system atrophy, another atypical parkinsonian syndrome.

Diagnosis of the underlying cause of CBS can only definitively be made postmortem, and given the degree of clinical-pathologic mismatch that exists, the term CBS should be used to describe the antemortem clinical syndrome in all cases. Given this diagnostic challenge, efforts have been directed at identifying biomarkers (e.g., CSF proteins, imaging, genetic) that can predict pathology in patients with CBS.

Genetics

The overlap between CBS, PSP, AD, and FTD based on clinical, imaging, and pathologic findings has been strengthened by genetic data. While monogenic forms of these disorders are rare, familial aggregation of CBS and PSP has been reported,^{e18} and occurrence of PSP in the sibling of a patient with CBD^{e19} lends support to the occurrence of a familial tauopathy. Progranulin mutations, initially identified in patients with tau-negative FTLT with ubiquitin inclusions on pathology (now known to have TDP-43 inclusions), may be a relatively common cause of familial CBS.^{e20} As mentioned, the contribution of single pathogenetic mutations to the pathophysiology of these neurodegenerative disorders is likely small, but of great relevance

In addition to immunohistochemical features that distinguish the different pathologic causes of CBS, distinct microscopic findings also characterize the neurodegenerative causes.

is the predisposition that may be imposed by single nucleotide polymorphisms in specific genes. For example, the H1 haplotype in the microtubule-associated protein tau (*MAPT*) gene is strongly associated with both PSP and CBD,^{e21} strengthening the consideration of these diseases as lying along a pathophysiologic spectrum. A specific vascular endothelial growth factor haplotype may also confer increased risk for CBS,^{e22} but the relevance of this will need to be taken in context of underlying pathology, which was unknown in many of the cases for which this genetic association was found.

Biomarkers in the evaluation of CBS

Most cases of CBS appear to be sporadic. Thus, it is necessary to develop other methods for establishing the pathology associated with CBS. There is growing emphasis on disease-specific biomarkers as aids in the antemortem diagnosis of neurodegenerative disorders. While biomarkers for many of the causes of CBS, such as CBD, PSP, and AD, have yet to be validated, candidate biomarkers include those derived from CSF testing and various imaging modalities.

CSF in the evaluation of CBS In interpreting results of biomarker studies in neurodegenerative disorders, it is key to recognize that the majority of studies are limited by the lack of pathologic diagnosis. For example, a recent study^{e23} found that while CSF total and phosphorylated tau discriminated CBS from PD, these tests were not helpful in distinguishing CBS from PSP. However, since the underlying pathology was not known, and since it is probable that some CBS cases were due to PSP pathology, no firm conclusions can be drawn from this study. Several other studies have examined CSF tau in CBS cases,^{e24–e27} but only a few small studies have examined CSF tau in patients with pathologically confirmed diagnoses.^{e28} Of particular interest given the frequency of AD pathology in CBS cases is that a high CSF tau:amyloid- β ratio may be useful in distinguishing AD from other causes of CBS (e.g., frontotemporal lobar degeneration [FTLD])^{e28,e29} (note an overlap in cases reported in these 2 references). Confirmation in larger studies is needed.

Imaging in the evaluation of CBS While there are as yet no imaging tests that can definitively identify underlying pathology in CBS, specific patterns of atrophy on MRI may be useful. For example, using MRI voxel-based morphometry, greater temporoparietal atrophy—particularly posterior temporal and inferior parietal regions, as well as the precuneus—suggests underlying AD pathology,^{8,e30,e31} whereas midbrain and superior cerebellar peduncle atrophy suggests PSP.^{e32} Focal atrophy in premotor cortex and the supplementary motor area on routine MRI^{e31} or frontoparietal lobe and pallidal atrophy in the absence of brainstem atrophy using MRI voxel-based morphometry^{e32} may suggest CBD. Although MRI, including diffusion tensor imaging,^{e33} has also been used to investigate white matter changes in CBS,^{e33–e35} we are not aware of reports involving CBS cases with known pathology.^{8,e32} Ultimately, multimodality imaging, assessing both gray and white matter structural changes, with incorporation of MRI quantitation (which provides information about tissue microstructure), may prove superior in predicting underlying pathology in CBS relative to either type of imaging alone.

Ligand-based nuclear imaging is another imaging modality that warrants further investigation as a tool to distinguish between different neurodegenerative disorders. Like the CSF tau:amyloid- β ratio described above, amyloid imaging may be of particular value in

Corticobasal syndrome: Five new things

- The term CBS should be used to describe the antemortem clinical syndrome
- There are no specific clinical features that reliably predict underlying pathology in CBS
- Recent efforts have been directed at identifying biomarkers (e.g., CSF proteins, imaging) that can predict pathology in patients with CBS, and definitive diagnosis of the underlying cause of CBS can only be made postmortem
- Specific single nucleotide polymorphisms may contribute to the risk of several causes of CBS, including PSP and CBD
- While predicting the specific underlying pathology in CBS has proven difficult, the vast majority of cases presenting with CBS can be accurately classified as tauopathies, and as such may benefit from tau-targeted therapies in the near future

determining which CBS cases are due to underlying AD pathology. Tau-based ligand imaging is under active investigation.^{e36,e37} PET and single photon emission tomography using presynaptic and postsynaptic radioligands to components of the dopaminergic system (dopamine transporters or receptors, or both) are also of particular interest.^{e38–e40} Finally, studies of regional metabolic changes using fluorodeoxyglucose PET,^{e41} in addition to noninvasive hemodynamic assessment (through magnetic resonance or CT perfusion or newer techniques such as arterial spin labeling MRI) may be of utility in CBS as well. Application of all these imaging modalities to pathologically confirmed cases is required to further define their role.

The tauopathy spectrum

The designation of tauopathy, defined as a neurodegenerative disorder characterized pathologically by the presence of neuronal and glial deposits of tau protein, encompasses CBD, PSP, Pick disease, and other forms of tau-related FTLN including FTLN associated with *MAPT* mutations.^{e42,e43} The clinical and pathologic overlap between CBD and other tauopathies has led CBD to be grouped with these other conditions under the pathologic rubric of FTLN-tau.^{e42,e44}

While predicting the specific underlying pathology in CBS has proven difficult, data suggest that predicting an underlying tauopathy on clinical grounds may be achieved with relatively high sensitivity,^{14,e45} although longitudinal data are lacking. It has been estimated that 83% of cases presenting with CBS can

be accurately classified as tauopathies.^{e45} Tau-negative CBS may have a younger age at onset,¹⁴ although others have demonstrated shorter disease duration in tauopathies.^{e46}

The phenotype of neurodegenerative disorders relates in large part to the anatomic distribution of the underlying pathology rather than the underlying pathology per se.^{e45} Several lines of evidence suggest that CBD, PSP, and FTLN lie along a spectrum, with shared clinical, genetic, and pathologic findings. Moreover, AD can present in protean fashions, including CBS. While clinical characterization continues to be an important part of neurology, incorporation of imaging, biochemical, and genetic markers into disease classification will be essential for accurate diagnosis and appropriate patient selection for clinical trials, particularly those targeting specific underlying proteinopathies such as a tauopathy.

DISCUSSION

Understanding of CBS has evolved dramatically since its description over 40 years ago. While certain features have traditionally been associated with this condition, a wide spectrum of clinical presentations can occur, ranging from purely motor to predominantly cognitive and language-related syndromes. CSF, imaging, and genetic markers are likely to be of great utility in predicting risk for and diagnosis of the underlying neurodegenerative disorders implicated in CBS. The key to establishing these as reliable diagnostic tests will be further studied in clinically well-characterized patients with known pathology. The underlying proteinopathy in many causes of CBS is tau-related, and in the future, tau-targeted therapeutics will benefit many patients with CBS. Correctly identifying those patients who may benefit from such interventions will be essential for therapeutic success.

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