

Corticobasal Degeneration

The Syndrome and the Disease

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INTRODUCTION

In 1967, Rebeiz, Kolodny, and Richardson described three patients with a progressive asymmetric akinetic-rigid syndrome and apraxia and labeled these cases as “corticodentatonigral degeneration with neuronal achromasia” (1,2). Additional reports on this disorder were almost nonexistent until the early 1990s. Over the past 10 yr, interest in this disorder has increased markedly. The nomenclature has also undergone evolution. The core clinical features that have been considered characteristic of the disorder include progressive asymmetric rigidity and apraxia, with other findings suggesting additional cortical (e.g., alien limb phenomena, cortical sensory loss, myoclonus, mirror movements) and basal ganglionic (e.g., bradykinesia, dystonia, tremor) dysfunction.

The characteristic findings at autopsy have been asymmetric cortical atrophy, which is typically maximal in the frontoparietal regions, basal ganglia degeneration, and nigral degeneration. Microscopically, swollen neurons that do not stain with conventional hematoxylin/eosin (so-called ballooned, achromatic neurons) are found in the cortex. Abnormal accumulations of the microtubule-associated tau protein are found in both neurons and glia.

In this chapter, the concepts and data relating to the corticobasal syndrome and corticobasal degeneration as presented in a recent review (3) are expanded.

NOMENCLATURE

The terminology relating to corticobasal degeneration (CBD) has been confusing. The following terms have been used: *corticodentatonigral degeneration with neuronal achromasia* (1,2), *corticonigral degeneration* (CND) (4), *cortical-basal ganglionic degeneration* (CBGD) (5), *corticobasal ganglionic degeneration* (CBGD) (6), and *corticobasal degeneration* (CBD) (7). Analyses from several academic centers have shown that the constellation of clinical features originally considered characteristic of this disorder can be seen in several non-CBD disorders, leading others to suggest syndromic terms such as *corticobasal syndrome* (3), *corticobasal degeneration syndrome* (8), *Pick complex* (9), *progressive asymmetric rigidity and apraxia* (PARA) *syndrome* (10), and *asymmetric cortical degeneration syndrome–perceptual-motor type* (11). Consensus on the terminology has not been established. In this review, the term *corticobasal syndrome* (and abbreviation CBS) will be used to characterize the constellation of clinical features initially considered characteristic of corticobasal degeneration, and the term *corticobasal degeneration* (and abbreviation CBD) will be used for the histopathologic disorder.

DEMOGRAPHICS AND EPIDEMIOLOGY

Like many other neurodegenerative disorders, symptoms usually begin insidiously in the sixth to eighth decade and gradually progress over 3–15 yr until death. Males and females are equally affected. A defining characteristic of the CBS is asymmetric limb findings, but there does not appear to be any predilection to the right or left side. A relatively high frequency of coexisting autoimmune diseases was noted in one series (12). This is a sporadic disorder, although there are rare reports of a similarly affected relative (13).

The incidence and prevalence of the CBS and CBD are not known. Bower et al. did not identify any case of CBS or CBD in their analysis of parkinsonism in Olmsted County, Minnesota (14). However, in a review of the autopsy records of the Mayo Clinic from 1970 to 2000, two residents of Olmsted County, Minnesota, were found to have CBD pathology, with one exhibiting the CBS and the other exhibiting dementia of the Alzheimer type (B. Boeve, unpublished data). As of 2003, we are following 11 patients with the CBS in the Mayo Alzheimer's Disease Research Center who reside in the state of Minnesota. Considering there are approx 5 million residents in the state, a minimum prevalence estimate is at least 2 per million (B. Boeve, unpublished data). The rarity of the CBS and CBD will make more definitive incidence and prevalence estimates difficult.

CLINICAL FEATURES OF THE CORTICOBASAL SYNDROME

Details regarding the specific clinical features of the CBS can be found in several sources (3,5,10,12,15–17).

Progressive Asymmetric Rigidity and Apraxia

The core clinical features are progressive asymmetric rigidity and apraxia. Symptoms typically begin in one limb, with no apparent predilection for the right or left side. Patients describe their limb as “clumsy,” “incoordinated,” or “stiff.” On examination the limb is mildly to severely rigid, and sometimes adopts a dystonic posture. Features of both rigidity (i.e., velocity-independent increased tone) and spasticity (i.e., velocity-dependent increased tone) can be present in the affected limbs. Alternating motion rates are markedly reduced. The affected limb often becomes profoundly apraxic. Initially, the clumsiness and breakdown of complex coordinated movements may represent limb-kinetic apraxia. However, this is difficult to completely distinguish from the effects of basal ganglia dysfunction including rigidity, bradykinesia, and dystonia. Later, clear features of ideomotor apraxia develop with the inability to correctly perform or imitate gestures and simple activities. When asked to perform these activities or gestures with an involved hand, patients often glare at the limb in question and visibly struggle. With time, the limb becomes completely useless, and other limbs become similarly affected. Typically, progressive asymmetric rigidity and apraxia is present in one of the upper limbs for at least 2 yr, then either the ipsilateral lower limb or contralateral upper limb becomes involved, eventually leading to severe generalized disability several years later. Less commonly, a lower limb is affected first, or progression occurs rapidly over many months.

Apraxia and rigidity have undergone further study. Leiguarda et al. evaluated buccofacial, ideomotor, and ideational praxis in 10 patients with the CBS (18). Their findings suggested that ideomotor apraxia was the most common type of apraxia in the CBS, and likely reflected dysfunction of the supplementary motor area. Those who had coexisting ideational apraxia correlated with global cognitive impairment, which suggested additional parietal or more diffuse cortical dysfunction (18). Caselli et al. compared detailed kinematic data in several patients with the CBS, including one case who had CBD at autopsy and another who had Alzheimer's disease (AD) (19). Severe abnormalities in temporal and spatial control, motor programming, and intermanual symmetry were present regardless of the presence or absence of dementia or specific histology (19). Boeve et al. studied two siblings with a familial neurodegenerative disorder associated with nonspecific histopathology, in which one brother exhibited the CBS during life whereas the other had classic frontotemporal dementia

(FTD) features (20). The case with the CBS features had no significant degenerative changes in the basal ganglia and substantia nigra, suggesting that extrapyramidal dysfunction can exist in the absence of appreciable pathology in the nigrostriatal system (20). Hence, additional clinical, radiologic, and pathologic studies are necessary to better define the anatomic substrates underlying apraxia and rigidity in the CBS.

Alien Limb Phenomenon

The alien limb phenomenon is an intriguing feature in the CBS. Patients often describe their affected limb as “alien,” “uncontrollable,” or “having a mind of its own,” and often label the limb as “it” when describing the limb’s behavior. The movements are spontaneous and minimally affected by mental effort, sometimes requiring restraint by the contralateral limb. This phenomenon often lasts a few months to a few years before progressive rigidity or dystonia supercedes.

There has been debate as to what constitutes true alien behavior from pseudoathetosis owing to cortical sensory loss to simple levitation of a limb (21–25). This phenomenon likely relates to pathology in the supplementary motor area and the efferent/afferent connections.

Cortical Sensory Loss

Cortical sensory loss is often manifested symptomatically as “numbness” or “tingling.” Impaired joint position sense, impaired two-point discrimination, agraphesthesia, and astereognosis in the setting of intact primary sensory modalities are all evidence of cortical sensory loss. This likely relates to pathology in somatosensory cortex \pm thalamus.

Myoclonus

Myoclonus, if present, usually begins distally in one upper limb and may spread proximally. The frequency and amplitude of myoclonic jerks typically increase with tactile stimulation (i.e., stimulus-sensitive myoclonus) and action (i.e., action myoclonus). Recent electrophysiologic studies suggest that the myoclonus in this disorder results from enhanced direct sensory input to cortical motor areas. Typically, a peripheral stimulus inducing myoclonic jerks is not associated with an enhanced somatosensory evoked potential (SSEP) and the latency from stimulus to jerk is brief, just sufficient to have reached the cortex and returned to the periphery (i.e., ~ 40 ms in the upper limb). These features are distinct from most other forms of cortical reflex myoclonus (which is associated with enlarged SSEPs and a longer stimulus-to-jerk latency) (26,27).

Mirror Movements

Mirror movements are present if the opposite limb involuntarily performs the same activity as the one being examined. Mirror movements are often suppressible, but when the individual is distracted and rechallenged with the same maneuver several minutes later, they will recur. Patients also frequently demonstrate overflow movements on the same side of the body, whereby attempted movement in an arm or leg causes additional movement in the ipsilateral limb, including elevation, mirroring, etc. Mirror movements have been associated with the alien hand syndrome (28), although many patients have them without alien limb features. Mirror movements are often found on examination but are rarely symptomatic.

Dystonia

Dystonic posturing of a limb is a common early manifestation, usually affecting one upper limb. Frequently, the posturing of the hand takes on a “fisted” appearance, although hyperextension of one or more fingers may occur. Initially, dystonia may only be evident during walking or reaching. In those with symptoms beginning in a lower limb, the foot is often tonically inverted, and ambulation is severely limited. Pain often but not always accompanies dystonia. The “fisted hand sign” may represent one of the most specific clinical features for underlying CBD in the CBS (Rippon et al., unpublished data).

Tremor

Tremor is another common presenting feature, and patients typically describe the affected extremity as “jerky.” A postural and action tremor often evolves to a more jerky tremor and then to myoclonus. Unlike the tremor of Parkinson’s disease (PD), which is most prominent at rest and dampens with action, the tremor is amplified with activity and minimal at rest. A classical 4- to 6-Hz parkinsonian rest tremor is rarely, if ever, evident in this disorder.

Lack of Levodopa Response

There are no published cases in which a significant and sustained clinical improvement has occurred with levodopa therapy (29). Many regard the lack of objective improvement during therapy with at least 750 mg of daily levodopa (divided doses, on an empty stomach) as a diagnostic feature of the disorder (realizing that other akinetic-rigid syndromes fail to respond to levodopa as well).

Dementia

Clinically significant dementia is not a typical early finding in patients with the CBS, but impairment in one or more cognitive domains is often present. However, it should be emphasized that the absence of early clinically significant dementia relates largely to the application of diagnostic criteria that have attempted to exclude other disorders such as AD and Lewy body dementia. In fact, as discussed below, although the pathology of CBD may be the most common cause of the CBS, some studies have found that it presents more commonly as a dementia syndrome (30).

Yes/No Reversals

A very intriguing feature in the CBS (as well as other disorders) is the tendency for patients to shake their head and respond “yes” when they actually mean “no,” and vice versa (31). Whereas some patients and relatives describe this phenomenon spontaneously, this often requires specific questioning by the clinician. Relatives and friends of affected patients tend to repeat their questions, or ask “do you really mean yes or no?” and thus this issue can significantly affect communication in some patients. This phenomenon is likely due to frontosubcortical dysfunction, in which mental flexibility and inhibitory control is impaired (31).

Focal or Lateralized Cognitive Features

Aphasia (which is typically nonfluent) (32), ideomotor apraxia, hemineglect, etc., are lateralized cognitive features that are as frequent as the motor features. Apraxia of speech and/or nonverbal oral apraxia are quite common; in fact, one published case presented with speech apraxia and did not develop other “typical” features until at least 5 yr later (33). Although rarely symptomatic, patients often demonstrate constructional dyspraxia on drawing tasks, particularly if the parietal lobe of the nondominant hemisphere is sufficiently affected. Other nondominant parietal lobe findings such as hemineglect and poor spatial orientation can also occur, which often are symptomatic in activities of daily living. Apraxic agraphia may result if the homologous region of the dominant hemisphere is dysfunctional. The lack of these findings being noted in the CBD literature probably stems from clinicians not including assessment of visuospatial/visuoperceptual functioning and neglect (11,16).

Neuropsychiatric Features

Depression, obsessive-compulsive symptomatology, and “frontal” behavioral disturbances can occur in the CBS syndrome (34,35). Visual hallucinations and delusions are very rare. The presence of visual hallucinations in the setting of cognitive impairment and/or parkinsonism may therefore favor a diagnosis of Lewy body disease rather than CBD (36,37).

Ocular Motor Apraxia

Ocular motor apraxia occurs to some degree in almost every patient (17). This includes difficulty initiating saccades and voluntary gaze, but pursuit and optokinetic nystagmus are typically preserved. In contrast to patients with progressive supranuclear palsy (PSP), those with the CBS have normal speed and amplitude of the saccades. On the other hand, eventually patients may develop supranuclear gaze paresis that can be indistinguishable from that seen in PSP. Eyelid opening/closing apraxia is also frequent.

Other Findings

Several other less specific findings may also occur. Frontal release signs, hypokinetic dysarthria, asymmetric hyperreflexia, and/or extensor toe responses also occur with some frequency. Postural instability is very common later in the disease and may be related to gait apraxia, bilateral lowerlimb parkinsonian, dystonia, or less frequently vestibular involvement. If balance problems are present at an early stage, they are usually secondary to lower-limb involvement at onset. Appendicular ataxia, chorea, and blepharospasm are infrequent manifestations. Dysphagia begins insidiously in the later stages of the disease in contrast to what usually occurs in PSP, and as in that disorder eventually leads to aspiration pneumonia and death in most instances.

DIAGNOSTIC CRITERIA

Four sets of clinical diagnostic criteria have been published (3,5,38,39) (Tables 1-4). The criteria by Maraganore et al., Lang et al., and Kumar et al. are similar to other sets of criteria (e.g., AD, ref. 40, PSP, ref. 41; etc.) in which those clinical features that are thought to best predict underlying CBD are listed and qualified. Yet, several investigators have shown considerable clinicopathologic heterogeneity in patients clinically suspected to have CBD (42-44). The criteria proposed by Boeve et al. takes this heterogeneity into account and lists the clinical features for the *syndrome*, which is conceptually similar to the syndromes of frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia (45). None of these sets of criteria have been rigorously validated, and refinements are likely to be necessary.

Consensus was reached for the neuropathologic criteria for the diagnosis of CBD (46). The core features are listed in Table 5. A critical point is that appropriate staining techniques (i.e., Gallyas silver staining, immunocytochemistry with tau, and phospho-neurofilament or α -B-crystallin), should be performed in appropriate cases, particularly in those with dementia and/or parkinsonism where no significant Alzheimer or Lewy body pathology is found. More details on the neuropathologic findings in CBD are discussed below.

FINDINGS ON ANCILLARY TESTING

Many of the diagnostic studies available for evaluating brain disease have been studied in the CBS and CBD, and like so many other facets of the syndrome and the disorder, the findings are difficult to interpret. Most of the literature on the laboratory, neuropsychologic, electrophysiologic, and radiologic findings in CBD have involved patients with clinically diagnosed CBD (i.e., the CBS) but without pathologic confirmation. Since a considerable proportion of patients with the CBS (approx 50% in one series—see subheading Diagnostic Accuracy) have a non-CBD disorder underlying their symptoms, one must view the findings described below consistent with the CBS but as yet unproven for the disorder of CBD.

Laboratory Findings

Routine blood, urine, and cerebrospinal fluid (CSF) tests are typically normal. Recent studies indicate that the tau haplotype in CBD is similar to that in PSP (47). Elevation of tau in the CSF has also been identified in CBD patients (48). Whether the tau haplotype or CSF tau level improves antemortem diagnostic accuracy requires further study.

Table 1
Clinical Diagnosis of Corticobasal Degeneration: Criteria of Maraganore et al.

Clinically Possible CBD:

No identifiable cause (e.g., tumor, infarct), at least three of the following:

- Progressive course
- Asymmetric distribution “PARA” syndrome
- Rigidity
- Apraxia

Clinically Probable CBD:

All four of clinically possible criteria, no identifiable cause, at least two of the following:

- Focal or asymmetric appendicular dystonia
- Focal or asymmetric appendicular myoclonus
- Focal or asymmetric appendicular postural/action tremor
- Lack of levodopa response

Clinically Definite CBD:

Meets criteria for clinically probable CBD, at least one of the following:

- Alien limb phenomenon
- Cortical sensory loss
- Mirror movements

Supportive findings:

- Asymmetric amplitude on EEG
- Focal or asymmetric frontoparietal atrophy on CT or MRI
- Focal or asymmetric frontoparietal \pm basal ganglia hypoperfusion on SPECT
- Focal or asymmetric frontoparietal \pm basal ganglia hypometabolism on PET

From ref. 38.

Table 2
Clinical Diagnosis of Corticobasal Degeneration: Criteria of Lang et al.

Inclusion criteria:

- Rigidity plus one cortical sign (apraxia, cortical sensory loss, or alien limb phenomenon)
- or
- Asymmetric rigidity, dystonia, and focal reflex myoclonus

Qualifications of clinical features:

- Rigidity: easily detectable without reinforcement
- Apraxia: more than simple use of limb as object; clear absence of cognitive or motor deficit sufficient to explain disturbance
- Cortical sensory loss: preserved primary sensation; asymmetric
- Alien limb phenomenon: more than simple levitation
- Dystonia: focal in limb; present at rest at onset
- Myoclonus: reflex myoclonus spreads beyond stimulated digits

Exclusion criteria:

- Early dementia
- Early vertical-gaze palsy
- Rest tremor
- Severe autonomic disturbances
- Sustained responsiveness to levodopa
- Lesions on imaging studies indicating another pathologic process is responsible

From ref. 5.

Table 3
Clinical Diagnosis of Corticobasal Degeneration: Criteria of Kumar et al.

Core features:

- Chronic progressive course
 - Asymmetric at onset (includes speech dyspraxia, dysphasia)
- Presence of:
- “Higher” cortical dysfunction (apraxia, cortical sensory loss, or alien limb) and
 - Movement disorders (akinetic-rigid syndrome resistant to levodopa, and limb dystonia or spontaneous and reflex focal myoclonus)

Qualifications of clinical features:

Same as criteria of Lang et al.

Exclusion criteria:

Same as criteria of Lang et al.

From ref. 39.

Table 4
Proposed Criteria for the Diagnosis of the Corticobasal Syndrome

Core Features:

- Insidious onset and progressive course
- No identifiable cause (e.g., tumor, infarct)
- Cortical dysfunction as reflected by at least one of the following:
 - focal or asymmetric ideomotor apraxia
 - alien limb phenomenon
 - cortical sensory loss
 - visual or sensory hemineglect
 - constructional apraxia
 - focal or asymmetric myoclonus
 - apraxia of speech/nonfluent aphasia
- Extrapyramidal dysfunction as reflected by at least one of the following:
 - Focal or asymmetric appendicular rigidity lacking prominent and sustained levodopa response
 - Focal or asymmetric appendicular dystonia

Supportive Investigations:

- Variable degrees of focal or lateralized cognitive dysfunction, with relative preservation of learning and memory, on neuropsychometric testing
 - Focal or asymmetric atrophy on CT or MRI, typically maximal in parietofrontal cortex
 - Focal or asymmetric hypoperfusion on SPECT and hypometabolism on PET, typically maximal in parietofrontal cortex ± basal ganglia ± thalamus
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From ref. 3.

Table 5
Office of Rare Diseases Neuropathologic Criteria for the Diagnosis of Corticobasal Degeneration

Core Features:

- Focal cortical neuronal loss, most often in frontal, parietal, and/or temporal regions
- Substantia nigra neuronal loss
- Gallyas/tau-positive neuronal and glial lesions, especially astrocytic plaques and threads, in both white matter and gray matter, most often in superior frontal gyrus, superior parietal gyrus, pre- and postcentral gyri, and striatum

Supportive Features:

- Cortical atrophy, often with superficial spongiosis
 - Ballooned neurons, usually numerous in atrophic cortices
 - Tau-positive oligodendroglial coiled bodies
-

Adapted from ref. 46.

Neuropsychological Findings

Neuropsychometric testing typically shows impairment in those domains subserved by frontal/frontostriatal and parietal cognitive networks: attention/concentration, executive functions, verbal fluency, praxis, and visuospatial functioning (49,50). The profile of impairment depends in part on which cerebral hemisphere is maximally affected. Performance on tests of learning and memory tends to be mildly impaired if impaired at all. Alternative diagnoses, particularly AD, should be considered if performance on delayed recall and recognition measures are markedly abnormal.

It should be noted that the few published reports on the neuropsychological findings in CBD have involved clinically but not pathologically diagnosed cases, thus these patients had the CBS and may or may not have had underlying CBD. Since the diagnosis of CBS is based on the constellation of clinical features, which reflects the topography of dysfunction in the frontostriatal and parietal neural networks, the findings on neuropsychological testing should mirror this topography. Thus, the neuropsychological findings noted above should be considered typical of the CBS but not be considered diagnostic of underlying CBD.

Electrophysiologic Findings

Findings on electroencephalography (EEG) have varied from normal to marked dysrhythmic and delta slowing (51,52). Asymmetric amplitudes of background alpha activity and sleep spindles have been reported in the CBS (20).

The electrophysiologic aspects of myoclonus in cases of presumed CBD have been discussed in detail elsewhere (26,27), including the short reflex latency and reduced inhibition following magnetic stimulation over the cortex (53). Although there is at least one case of pathologically proven CBD who had a longer latency more typical of cortical reflex myoclonus, other cases of CBS with a long latency form of reflex myoclonus that have been studied have demonstrated other pathologies at postmortem (e.g., Pick's disease, AD, and motor neuron inclusion body dementia). In contrast, to date, the few cases coming to autopsy in which the short latency form was present in life have had the pathology of CBD (3). These findings may be the most specific antemortem predictor of underlying CBD identified thus far; however, many more cases need to be studied with clinical, electrophysiological, and pathological correlation.

Magnetic Resonance Imaging Findings

The purpose of performing a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain is to exclude a structural lesion such as a tumor, abscess, hematoma, or infarct. In

the absence of these lesions, some findings can be supportive of the diagnosis of CBS, such as asymmetric cortical atrophy, especially frontoparietal, with the more prominent atrophy existing contralateral to the side most severely affected clinically (54–59) (Fig. 1). The lateral ventricle in the maximally affected cerebral hemisphere can also be slightly larger than opposite one. Asymmetric atrophy in the cerebral peduncles may be present (5) (Fig. 2). Other reported MRI findings in the CBS include atrophy of the middle or posterior segment of the corpus callosum (60) (Fig. 3), hyperintense signal changes lateral to the putamen (54,56,61) (Fig. 4), atrophy of the putamen (61), and subtle hyperintense subcortical signal changes in motor \pm somatosensory cortex (62,63) (Fig. 5). These are often subtle findings and their presence or absence should not alter the clinical diagnosis of the CBS. Importantly, the majority of cases in which these MRI findings were identified have not had CBD verified postmortem. In the only series of patients with the CBS associated with CBD pathology, CBS associated with non-CBD pathology, and CBD pathology associated with non-CBS clinical features, none of these MRI findings were found to be adequately sensitive or specific for CBD—the disease (64).

Progressive parietal \pm frontal atrophy (Fig. 6) and thinning of the middle and posterior portion of the corpus callosum (Fig. 7) often occurs on serial MRI scans in patients with the CBS. Some patients present with a focal cortical degeneration syndrome such as frontotemporal dementia (Fig. 8), progressive aphasia, or posterior cortical atrophy (Fig. 9) and subsequently develop CBS findings.

We have also observed several atypical MRI findings in the CBS and CBD. Focal hyperintense subcortical signal changes can evolve (Figs. 10–12). The hazy or hyperintense signal changes may reflect gliosis and/or secondary demyelination. Some patients have minimal cortical atrophy, and despite unequivocal clinical progression, progressive atrophy is difficult to appreciate, although ventricular dilatation may be evident (Fig. 13). Increased signal along the parietofrontal cortical ribbon can be seen in patients with Creutzfeldt–Jakob disease who present with the CBS (Fig. 14).

Functional Neuroimaging Findings

Asymmetric hypoperfusion on single photon emission computed tomography (SPECT) and asymmetric hypometabolism on positron emission tomography (PET) involving the parietofrontal cortex \pm basal ganglia have been reported (65–71) (Fig. 15). Imaging of the nigrostriatal dopamine system typically demonstrates a reduction of striatal tracer uptake greater contralateral to the clinically most affected side. Unlike PD, uptake in the caudate is generally reduced to the same extent as in the putamen. However, these findings are not specific for CBD—the disease (72).

In summary, although the electrophysiologic findings in myoclonus and association of a specific tau haplotype and increased CSF tau are promising, there are no antemortem features or biologic markers identified to date that definitively distinguishes CBD from the CBD mimickers.

NEUROPATHOLOGIC FINDINGS

Consensus criteria for the pathologic diagnosis of CBD have recently been published (46) (Table 5).

Macroscopic

Asymmetric parietofrontal or frontotemporal cortical atrophy (Fig. 16), and pallor of the substantia nigra, are the typical macroscopic pathologic findings. Some individuals with typical clinical and microscopic findings do not have appreciable cortical atrophy, however.

Microscopic

Neuronal loss, gliosis, and superficial spongiosis are prominent in the maximally affected cortical gyri. Immunocytochemistry with tau as well as phosphorylated neurofilament or α B-crystallin is imperative when characterizing cases with possible CBD. The pathologic features of CBD—the disease include tau-positive (tau+) astrocytic plaques and tau+ threadlike lesions in gray and white

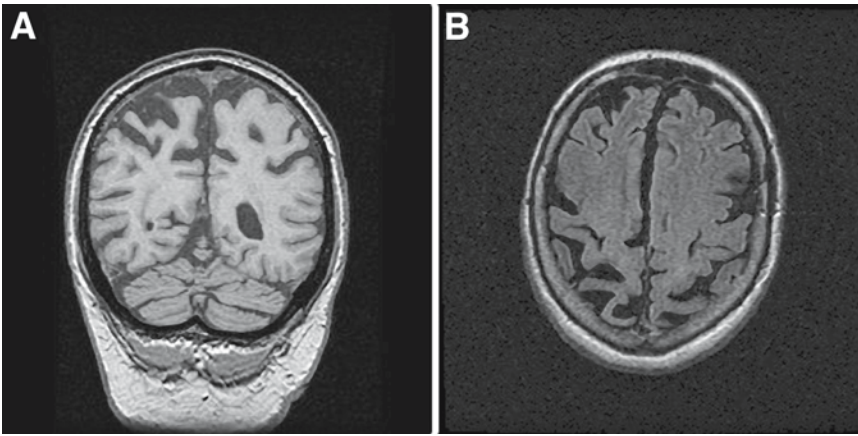


Fig.1. Coronal T1-weighted (A) and axial FLAIR (B) MR images in a patient with the corticobasal syndrome. Note the asymmetric parietal cortical atrophy, more evident in the right hemisphere in this patient.

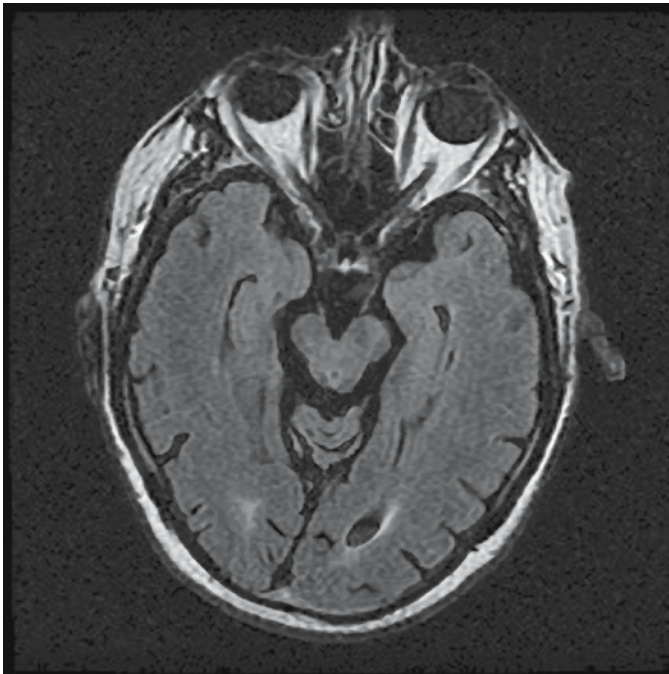


Fig. 2. Axial FLAIR MR image in a patient with the corticobasal syndrome, showing asymmetric atrophy of the cerebral peduncles.

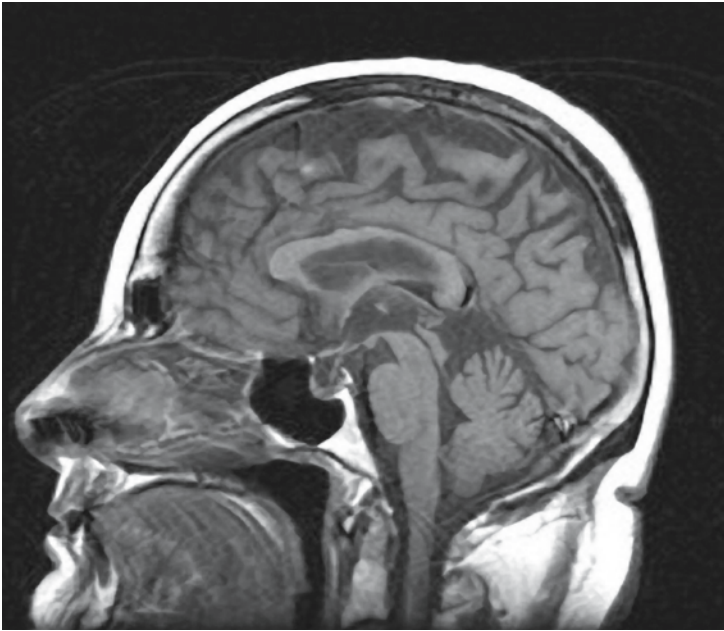


Fig. 3. Midsagittal T1-weighted MR image in a patient with the corticobasal syndrome, showing thinning of the corpus callosum where the projections between the parietal cortices traverse.

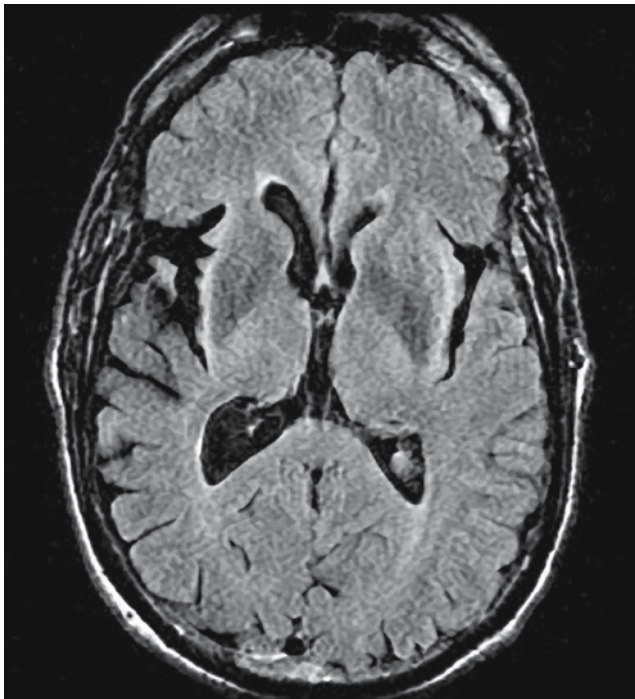


Fig. 4. Axial FLAIR MR image in a patient with the corticobasal syndrome, demonstrating the rare finding of increased signal lateral to the putamen.

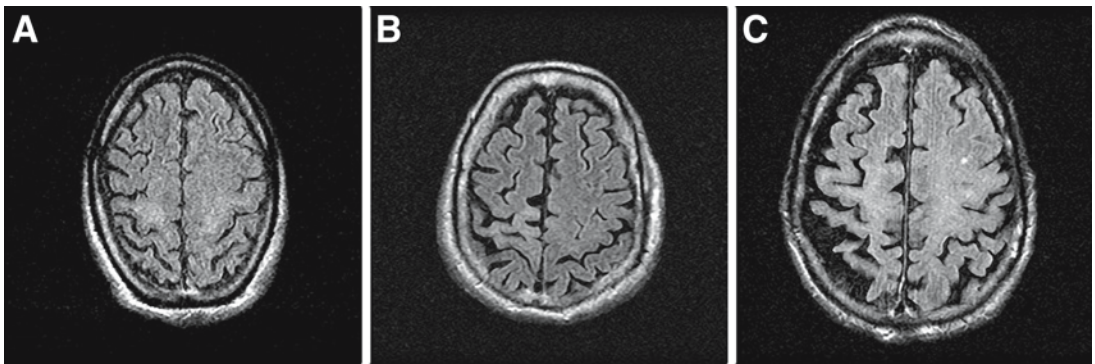


Fig. 5. Axial FLAIR MR images of three patients with the corticobasal syndrome, showing subtle, hazy increased signal in the subcortical posterior frontal/parietal white matter. The signal changes are asymmetric in **B** and **C**, but quite symmetric in **A** despite strikingly asymmetric clinical findings in all three patients.

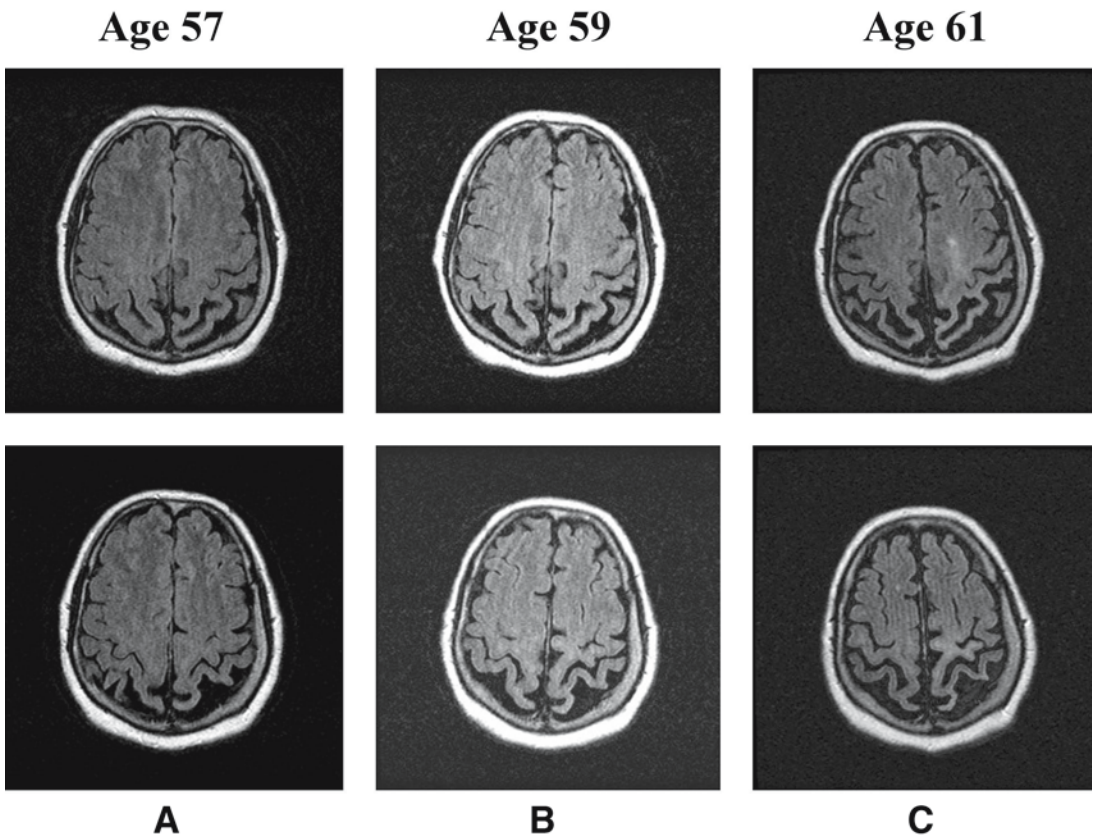


Fig. 6. Serial axial FLAIR MR images in a patient with the corticobasal syndrome. By age 61 (images in column **C**), she had also developed features of the Balint's syndrome.

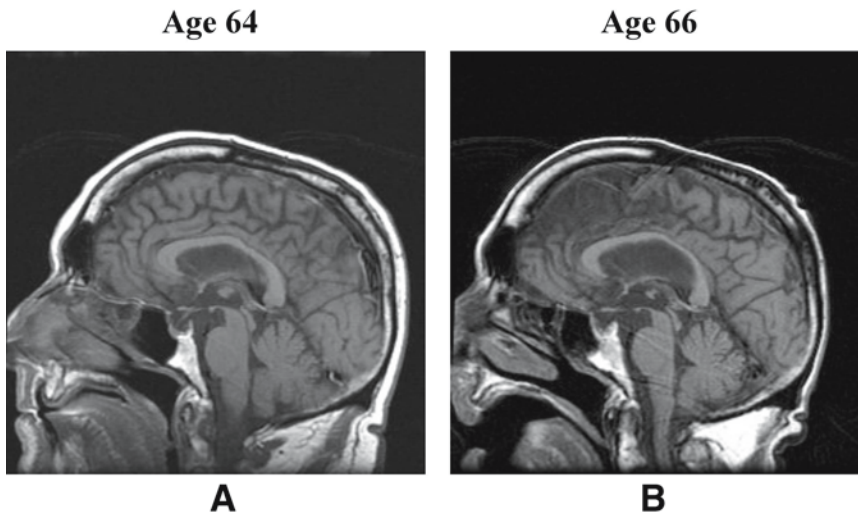


Fig. 7. Serial midsagittal MR images in a patient with the corticobasal syndrome. Note the progressive thinning of the posterior aspect of the corpus callosum (but sparing the splenium) and mild ventricular dilatation. The decreased signal along the mesial frontal region in B reflects evolving atrophy in this region.

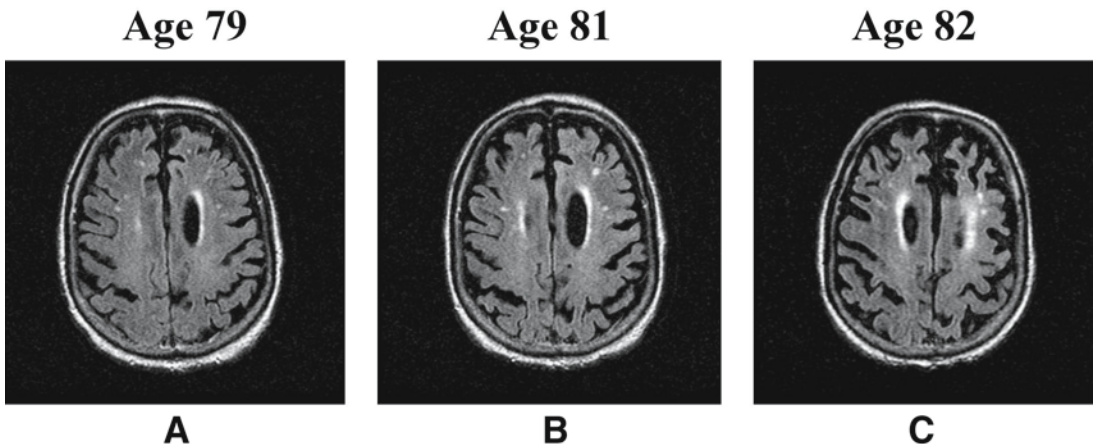


Fig. 8. Serial axial FLAIR MR images in a patient with features of frontotemporal dementia at age 79 (A), which then evolves to include nonfluent aphasia at age 81 (B) and corticobasal syndrome findings at age 82 (C).

matter, most often in superior frontal gyrus, superior parietal gyrus, pre- and postcentral gyri, and striatum (Fig. 17). Tau+ oligodendroglial coiled bodies are also common (Fig. 18). While achromatic, ballooned neurons that are immunoreactive to phosphorylated neurofilament or α B-crystallin are typically present in CBD (Fig. 19), their absence does not preclude the diagnosis of CBD if the appropriate tau+ lesions are present. These criteria have been validated (Litvan et al., in preparation).

These pathological features are indistinguishable from those in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) (46). Thus, knowledge about the family history and molecular genetics is necessary to adequately classify cases with CBD-type pathology.

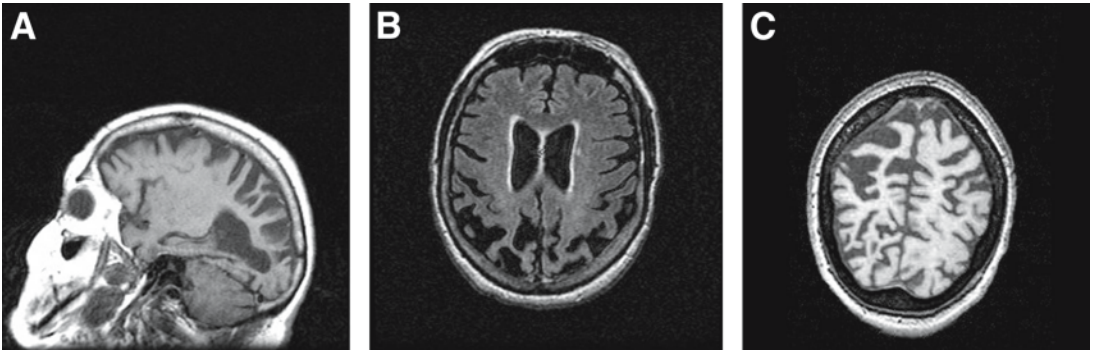


Fig. 9. Sagittal T1-weighted (A), axial FLAIR (B), and coronal T1-weighted (C) MR images in a patient who presented with the posterior cortical atrophy syndrome (i.e., Balint's syndrome, Gerstmann's syndrome, etc.) and subsequently developed classic corticobasal syndrome features.

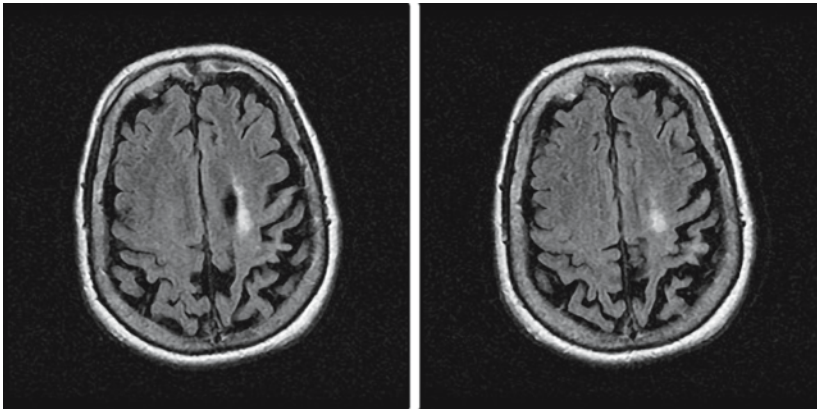


Fig. 10. Axial FLAIR MR images in a patient with the corticobasal syndrome, showing focal increased signal in the left posterior frontal white matter. Autopsy revealed corticobasal degeneration with significant tau-positive glial pathology in this region.

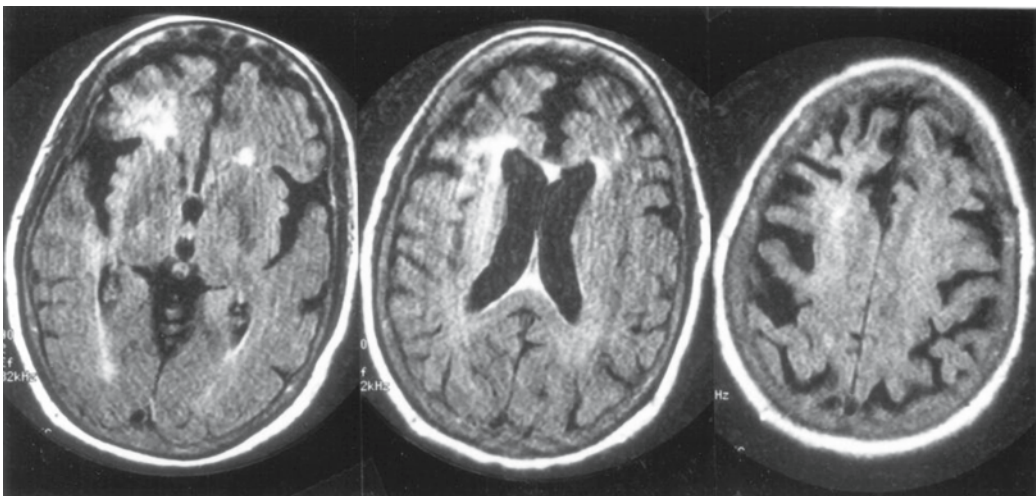


Fig. 11. Axial FLAIR MR images in a patient with the corticobasal syndrome, showing focal increased signal in the right frontal > parietal white matter. Autopsy revealed corticobasal degeneration with significant tau-positive glial pathology in this region.

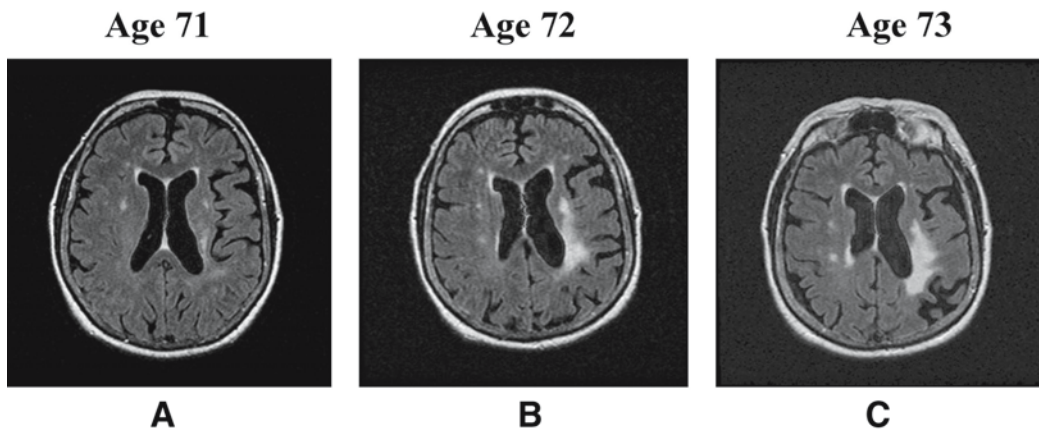


Fig. 12. Serial axial FLAIR MR images in a patient with the corticobasal syndrome, showing progressive focal increased signal evolving in the periventricular and subcortical white matter of the left parietal region.

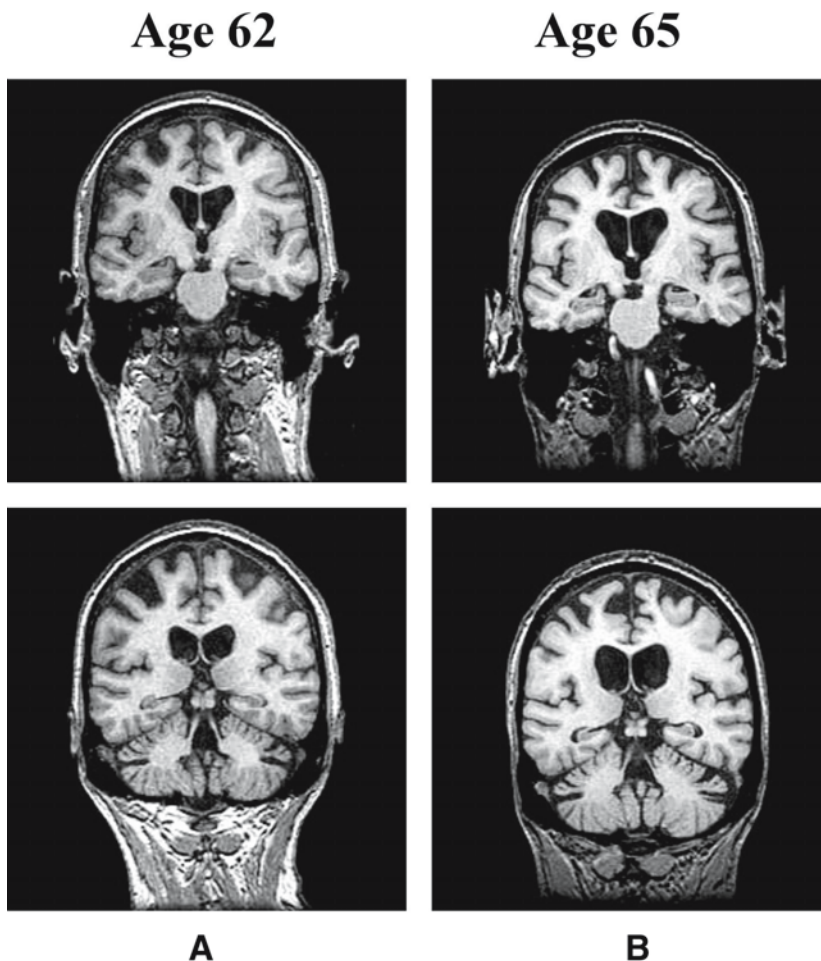


Fig. 13. Serial coronal T1-weighted images in a patient with the corticobasal syndrome at age 62 (A) and age 65 (B). Despite striking progression in her asymmetric CBS findings, note the rather mild and minimally progressive cerebral cortical atrophy over the frontal convexities. Mild progressive ventricular dilatation is evident, but the hippocampi do not appear significantly atrophic. This patient had progressive supranuclear palsy at autopsy.

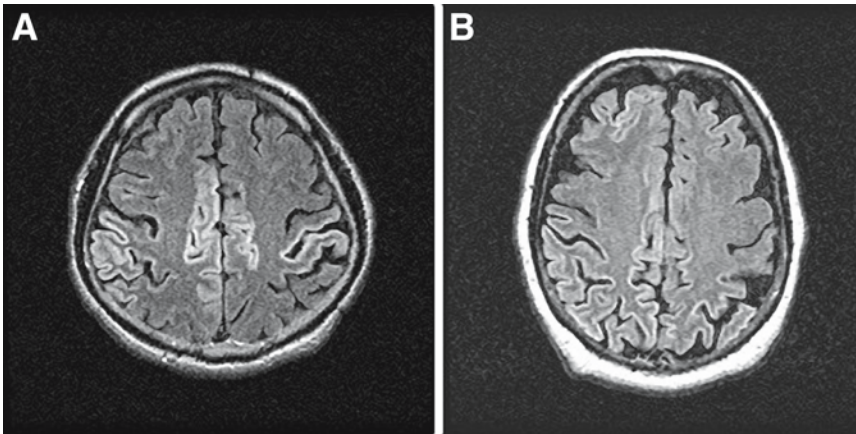


Fig. 14. Axial FLAIR MR images in two patients with the corticobasal syndrome. The patient in **A** has had a 3-yr course and is still alive, whereas the patient in **B** died after a 14-mo course. Note the striking increased signal along the cortical ribbon in the posterior frontal/parietal regions in both patients. Autopsy in patient **B** revealed Creutzfeldt–Jakob disease.



Fig. 15. Coronal single photon emission computed tomography (SPECT) images in a patient with the corticobasal syndrome. Note the hypoperfusion in the right frontoparietal > temporal cortex as well as basal ganglia and thalamus. Autopsy confirmed corticobasal degeneration in this patient.

CLINICAL FEATURES OF CORTICOBASAL DEGENERATION: THE DISEASE

There are few reports in which the clinical features in pathologically proven CBD have been characterized. Caselli et al. found subtle differences in kinematic abnormalities in a pathologically proven case of CBD compared to a patient with CBS who had AD pathology (19). The speech and language abnormalities associated with pathologically confirmed CBD have recently been described (73). Symptoms and signs of speech or language dysfunction were among the presenting features in over half of the patients in this series. Among these 13 cases, the features included dysarthria ($n = 4$; hypokinetic, spastic, ataxic, and mixed forms), apraxia of speech ($n = 5$), and aphasia ($n = 7$; fluent, nonfluent, and mixed forms). Hence, speech and language dysfunction is common in CBD, and the findings include variable degrees of dysarthria, apraxia of speech, and aphasia (73).



Fig. 16. Photograph of the brain of a patient with corticobasal degeneration who had exhibited classic corticobasal syndrome features antemortem. Note the cortical atrophy is maximal in the posterior frontal and parietal region. Courtesy Joseph E. Parisi, MD, Mayo Clinic, Rochester, Minnesota.

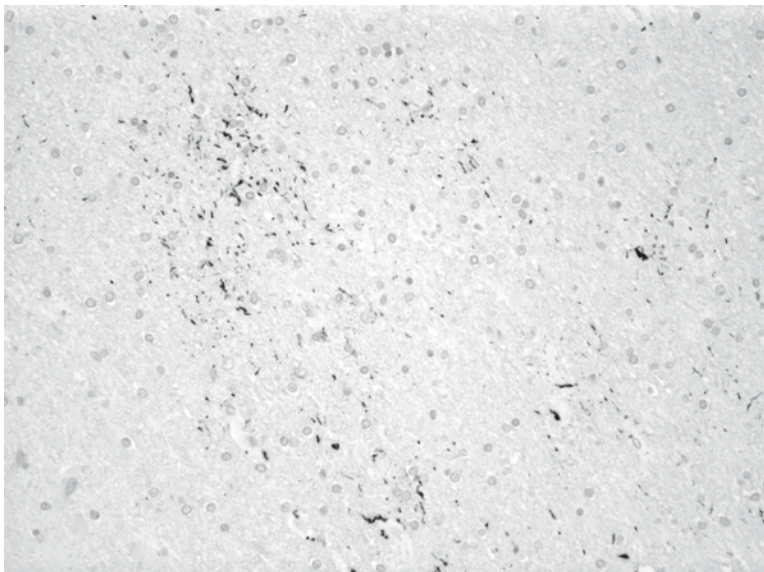


Fig. 17. Photomicrograph of parietal cortex with tau immunocytochemistry ($\times 20$) in a patient with corticobasal degeneration. Note the tau-positive threads and clusters of tau-positive astrocytes (“astrocytic plaques”) typical of CBD. Courtesy Joseph E. Parisi, MD, Mayo Clinic, Rochester, Minnesota.

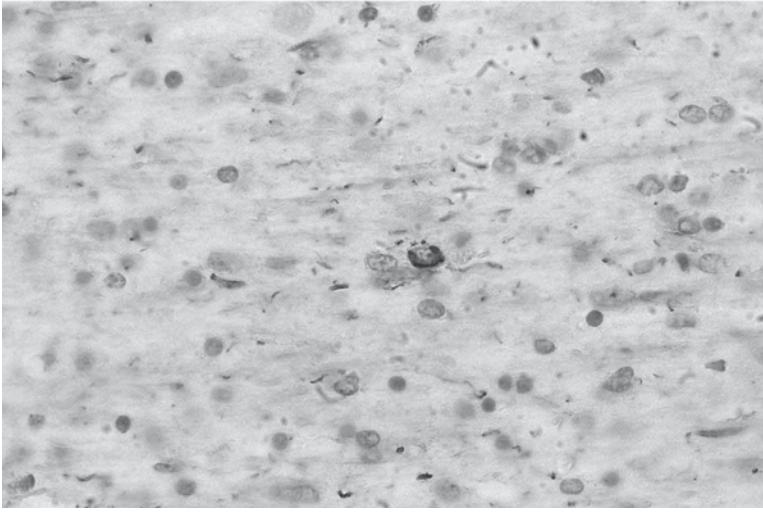


Fig. 18. Photomicrograph of subcortical frontal white matter with tau immunocytochemistry (x60) in a patient with corticobasal degeneration. Note the coiled or comma-shaped appearance of the inclusion characteristic of an “oligodendroglial coiled body.” Courtesy Joseph E. Parisi, MD, Mayo Clinic, Rochester, Minnesota.

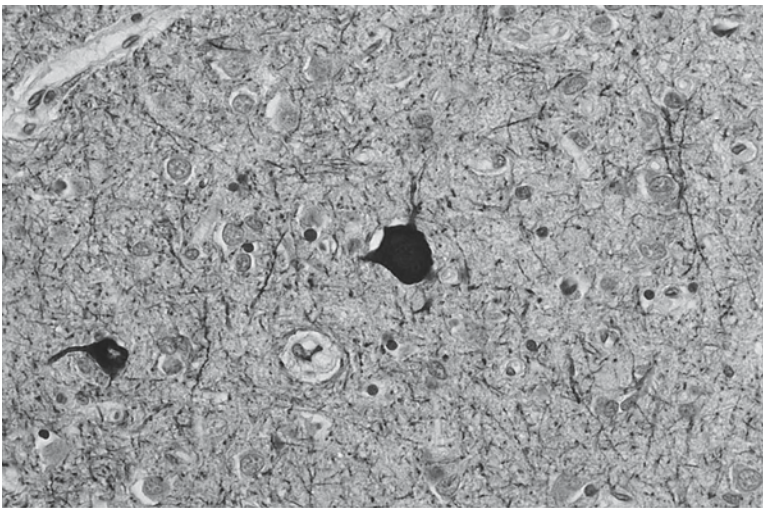


Fig. 19. Photomicrograph of parietal cortex with phosphorylated-neurofilament immunocytochemistry (x60) in a patient with corticobasal degeneration. Note the intense staining in a “ballooned” neuron typical of CBD. Courtesy Joseph E. Parisi, MD, Mayo Clinic, Rochester, Minnesota.

Table 6
Pathologic Diagnoses in 36 Consecutive Autopsied Cases
at the Mayo Clinic With the Corticobasal Syndrome

Diagnosis	No. of cases
Corticobasal degeneration	18
Progressive supranuclear palsy	6
Alzheimer's disease	4
Creutzfeldt–Jakob disease	3
Nonspecific degenerative changes	3
Pick's disease	1
Combined Alzheimer's disease/Pick's disease	1

Table 7
Clinical Diagnoses in 32 Consecutive Autopsied Cases
at the Mayo Clinic With Pathologically Proven CBD

Initial Clinical Diagnosis		Final Clinical Diagnosis	
10	Corticobasal degeneration	18	Corticobasal degeneration
6	Atypical Parkinson's disease	7	Progressive supranuclear palsy
6	Dementia/Alzheimer's disease	4	Primary progressive aphasia
4	Primary progressive aphasia	1	Alzheimer's disease
2	Progressive supranuclear palsy	1	Dementia with Lewy bodies
1	Dementia with Lewy bodies	1	Marchiafava–Bignami disease
1	Marchiafava–Bignami disease		
1	Multiple sclerosis		
1	Stroke		

The disorder of CBD can also present as several clinical syndromes. In addition to the CBS, the reported focal/asymmetric cortical degeneration syndromes associated with CBD pathology include frontotemporal dementia (74–77), a progressive aphasia syndrome (fluent and nonfluent subtypes) (76–81), and posterior cortical atrophy (with some or all features of the Balint's syndrome) (82). Some patients have been diagnosed antemortem as probable AD (30, 77). In fact, dementia was the most common presentation of CBD in one series (30). Many patients have had clinical findings indistinguishable from PSP (44, 83–88). One patient presented with apraxia of speech and subsequently developed more typical CBD features (33). Another presented with obsessive-compulsive features and visual inattention (89). Hence, from the clinicopathologic perspective, CBD is a heterogeneous disorder.

CLINICOPATHOLOGIC HETEROGENEITY

Although the early literature on CBD suggested it was a distinct clinicopathologic entity, numerous case reports and small series clearly indicates considerable clinicopathologic heterogeneity in the CBS and CBD—the disease. An updated review of this heterogeneity from one institution (43, 90) is shown in Tables 6 and 7. Thus, the following disorders can underlie the CBS: CBD, AD, Pick's disease, PSP, dementia lacking distinctive histopathology, and Creutzfeldt–Jakob disease (43), as well as dementia with Lewy bodies (91), motor neuron inclusion body dementia (92), and neurofilament inclusion body dementia (93). As noted above, CBD can present clinically as the CBS, dementia (not otherwise specified), primary progressive aphasia, frontotemporal dementia, posterior cortical atro-

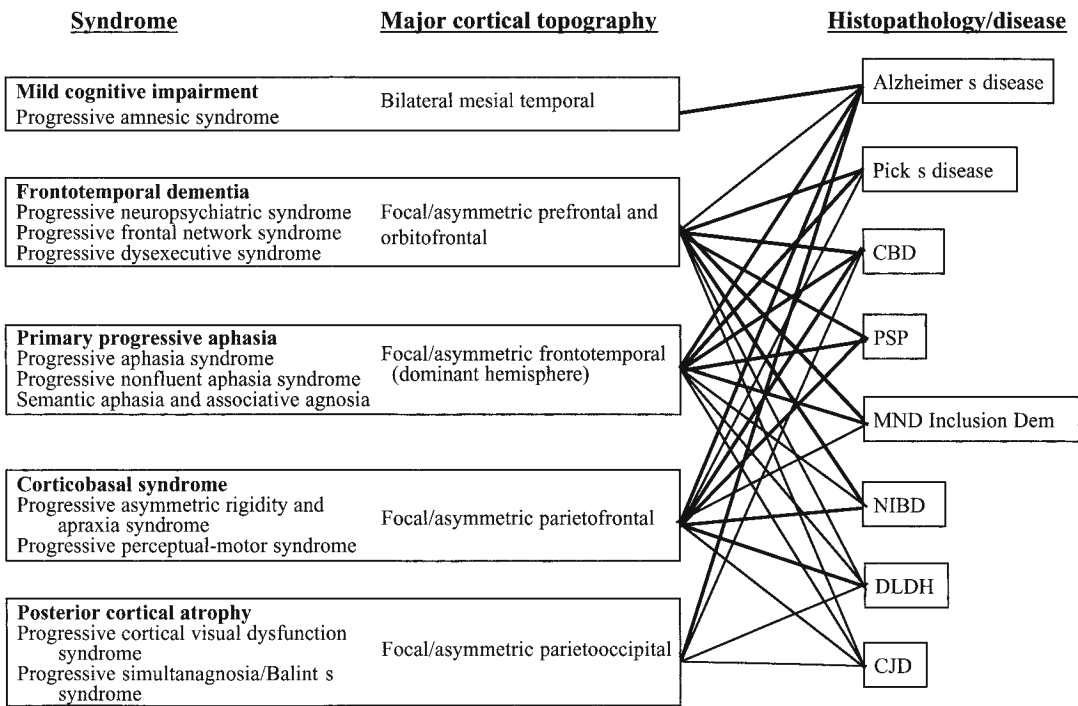


Fig. 20. Note the close syndrome-topography association for each syndrome, but the variable associated histopathologies for each syndrome. Darker lines signify associations that occur more frequently. Abbreviations: CBD, corticobasal degeneration; CJD, Creutzfeldt-Jacob disease; DLB, dementia with Lewy bodies; DLDH, dementia lacking distinctive histopathology; MND Inclusion Dem, motor neuron disease inclusion dementia; NIBD, neurofilament inclusion body dementia; PSP, progressive supranuclear palsy. Adapted from ref. 99.

phy, and progressive speech apraxia. Some patients often present with one of these focal cortical degeneration syndromes and subsequently develop features overlapping with one or more syndromes (8,9). Hence, it is now clear that in the CBS—like in the other focal/asymmetric cortical degeneration syndromes (11,94,95)—the clinical presentation and progression of symptoms reflect the topographic distribution of histopathology more so than the specific underlying disease. Furthermore, CBD has a variable pattern of cerebral cortical pathology, and the topographic distribution of pathology dictates the clinical presentation. A summary of the clinicopathologic correlations in the focal/asymmetric cortical degeneration syndromes is shown in Fig. 20. As therapies are developed that specifically target amyloid, tau, prion protein, synuclein, etc., pathophysiology, particularly if any such therapies have toxic side effects, improving the diagnostic accuracy of patients with the CBS and other focal/asymmetric cortical degeneration syndromes will become increasingly important.

DIAGNOSTIC ACCURACY

The clinicopathologic heterogeneity in CBS and CBD has led to relatively poor sensitivity and specificity for the diagnosis of CBD. As shown in Tables 6 and 7, among 36 consecutive patients with clinically suspected CBD (i.e., the CBS) who underwent autopsy, only half were found to have underlying CBD (specificity of the CBS for CBD = 50%). Furthermore, among 32 patients with pathologically proven CBD, only 18 exhibited the CBS (sensitivity of the CBS for CBD = 56%). Other investigators found high sensitivity but low specificity in the clinical diagnosis of CBD (96). This poor sensitivity and specificity has clearly stymied research in this area. However, if one views

the disorders as they relate to the putative dysfunctional protein, the specificity of the CBS for the tauopathies (considering AD as an amyloidopathy for this calculation) is 69%. Since some therapies that affect tau pathophysiology may have efficacy for any of the tauopathies, delineation of the specific histopathologic disorder may not be as important determining whether patients have a tauopathy underlying their symptoms. Clearly, biomarkers that are more sensitive and specific for CBD as well as the other tauopathies are needed.

PATHOPHYSIOLOGY

Several lines of evidence point toward dysfunction in microtubule-associated tau as a primary factor in the pathogenesis of CBD. The inclusions in glia and neurons are immunoreactive to tau (46). The pathology of CBD has been associated with mutations in tau (97). Transgenic mice with the P301L mutation have exhibited clinical and neuropathologic findings similar to humans (98). Hyperphosphorylation of tau disrupts binding to microtubules. Further characterization of the cascade of events involved in tau dysfunction and neurodegeneration will be critical to ultimately develop therapy.

MANAGEMENT

Since no therapy yet exists for CBD that affects the neurodegenerative process, management must be tailored toward symptoms. Pharmacotherapy directed toward parkinsonism has been disappointing (29). Levodopa, dopamine agonists, and baclofen tend to have little effect on rigidity, spasticity, bradykinesia, or tremor. However, levodopa should be titrated upward as tolerated to at least 750 mg per day in divided doses on an empty stomach to provide an adequate trial. Some patients have noted significant improvement in parkinsonism but this rarely persists beyond several months. In those who do improve dramatically with levodopa therapy, one must question whether CBD is the underlying disorder, as levodopa-refractory parkinsonism is considered by many to be a characteristic feature of the CBS and CBD. Anticholinergic agents rarely improve dystonia, and their use is limited by side effects. Botulinum toxin can alleviate pain owing to focal dystonia. Central pain has been rare, but some patients have responded to gabapentin. Tremor may respond initially to propranolol or primidone, but their effects wane with progression of the disorder. Clonazepam and/or gabapentin may reduce myoclonus in some cases. Although intuitively one would not consider any of the cholinesterase inhibitors to be beneficial in this disorder, we have seen rare cases who note improvement in psychomotor speed, concentration, and problem-solving abilities with donepezil, rivastigmine, or galantamine. Vitamin E and other antioxidant agents have been tried in hopes of delaying progression of the disorder, but there is no evidence yet supporting a disease-altering effect.

Because of the poor response to pharmacotherapy, the mainstay of management is therefore physical, occupational, and speech therapies. A home assessment by an occupational therapist can aid in determining which changes could be made to facilitate functional independence (e.g., replacing rotating doorknobs with handles; attaching specially formed pads around the handles of eating utensils and toothbrushes; purchasing clothing with velcro instead of buttons or laces, etc.). Passive range of motion (ROM) exercises minimize development of contractures, and all caregivers should be instructed to provide passive ROM exercises daily. In those who develop dystonic flexion of the hand musculature to form a "fisted hand," the fingernails can become imbedded in the palmar tissue leading to cellulitis and even osteomyelitis of the hand. One can avoid this by clipping the fingernails periodically, and by placing a rolled-up washcloth or hand towel in the palm of the hand. All patients experience gait impairment at some point during their illness. A walker with handbrakes can improve ambulation for some patients. Wheelchair and handicap privileges are warranted in essentially every patient. Use of a bedside commode is also worthwhile. Apraxia is often the most debilitating feature of the disorder, and this feature can complicate one's ability to operate a wheelchair or motorized scooter. However, many patients are able to learn to operate these devices and use them effectively

for months or years. We have seen a few patients whose “useless hand” was “made useful” by employing constraint-induced movement therapy. Some third-party payers have denied coverage for these devices and therapies, which is very unfortunate as any element of functional improvement and independence is important for these patients. Speech therapy and communication devices can optimize communication when dysarthria, apraxia of speech, or aphasia is present. Therapists also counsel patients and families on swallowing maneuvers and food additives to minimize aspiration when dysphagia occurs. Feeding gastrostomy should be discussed with all patients, although many decide not to undergo this procedure.

Some patients with the CBS develop elements of other focal cortical degeneration syndromes, such that features of frontotemporal dementia (FTD), primary progressive aphasia (PPA), posterior cortical atrophy (PCA), or some combination of these can evolve. Also, patients who present with one of these syndromes can develop features of the CBS. Management of many of these non-CBS syndromes is discussed elsewhere (99).

Other treatable comorbid illnesses must also be considered, most notably infections (e.g., pneumonia and urinary tract infections), psychiatric disorders, and sleep disorders. Although psychotic features rarely occur in the CBS, depression evolves in essentially every patient, likely owing in part to the preserved insight that is also characteristic of the disorder. Sleep disorders such as obstructive sleep apnea, central sleep apnea, restless legs syndrome, periodic limb movement disorder, etc. occur with some frequency in the CBS, and treatment can improve quality of life (100). REM sleep behavior disorder is very rare in the CBS; in fact if it is present, one must suspect some contribution of synucleinopathy pathology (101). Despite the difficulties of manipulating the headgear as part of nasal continuous positive airway pressure (CPAP) therapy owing to the limb apraxia, CPAP therapy for obstructive sleep apnea can be tolerated and used effectively in many patients. Patients and caregivers eventually require assistance in maintaining optimal care, which can be provided either through home health care or in a skilled nursing facility.

FUTURE DIRECTIONS

Clearly, with the CBS being no more than 60% sensitive and specific for CBD—the disease, further research in improving the antemortem diagnosis of CBD is necessary. No consensus yet exists for the diagnosis of the CBS. Further characterization of the natural history of patients with the CBS involving serial assessments of clinical, laboratory, neuropsychologic, and radiologic features is very important, as this information will be necessary to design future drug trials, particularly if agents active against tau pathophysiology are developed. Debate continues regarding whether CBD and PSP are variants of the same pathophysiologic process or distinctly separate disorders, and this warrants clarification. Additional studies on the rare kindreds with the clinical features of CBS (20,102) and/or pathologic features of CBD (13), whether associated with mutations in tau (i.e., FTDP-17) or not, may offer key insights as other genes impacting tau pathophysiology have yet to be identified. Finally, patients and their families should be encouraged to access sources of information and support as well as participate in research.

MAJOR ISSUES TO BE STUDIED IN THE FUTURE:

- Establish consensus criteria for the diagnosis of the CBS.
- Identify which clinical, laboratory, neuropsychologic, and neuroradiologic features are most predictive of underlying CBD in the CBS.
- Characterize the natural history of clinical, laboratory, neuropsychologic, and neuroradiologic findings in patients with the CBS to design future drug trials.
- Determine if CBD and PSP are distinct disorders or variants of the same pathophysiologic process.
- Identify kindreds with familial CBS and/or CBD.
- Identify genetic mechanisms involved in CBS and CBD pathogenesis.

WEBSITES

Caregivers Guide to Cortical Basal Ganglionic Degeneration (CBGD)

<http://www.tornadodesign.com/cbgd/>

NINDS Corticobasal Degeneration Information Page

http://www.ninds.nih.gov/health_and_medical/disorders/cortico_doc.htm

WEMOVE - Corticobasal Degeneration

<http://www.wemove.org/cbd.html>

Parkinson's Institute on Corticobasal Degeneration

http://www.parkinsonsinstitute.org/movement_disorders/corticobasal.html

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