

Corticobasal degeneration

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Corticobasal degeneration is a progressive neurodegenerative disease that typically presents with asymmetrical parkinsonism and cognitive dysfunction. Recent molecular advances have given some clues to the pathogenesis of the disease. Clinical diagnosis is complicated by both the variability of presentation of true corticobasal degeneration, for example as a dementing illness, and the syndromes that look like it but are caused by other neurodegenerative diseases. Although definitive diagnosis of corticobasal degeneration can only be made at post-mortem examination, recent advances in imaging can assist the clinician with diagnosis. Treatment options remain limited and mostly address symptoms.

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The first clear description of corticobasal degeneration was given in 1968 in the report by Rebeiz and colleagues¹ of three patients with slow and awkward voluntary limb movement, tremor, dystonic posturing, stiffness, lack of dexterity, “numbness or deadness” of the affected limb, and gait disorder. They described the disorder as “corticodentatonigral degeneration with neuronal achromasia” identified by asymmetrical frontoparietal cortical atrophy and neuronal loss, associated gliosis, and swelling of the neuronal cell bodies, which were devoid of Nissl substance (hence the term achromasia). There was substantial loss of pigmented neurons in the substantia nigra in all three patients, variable subcortical neuronal involvement, and secondary corticospinal tract degeneration. Since this report, many other clinical case series have used different names to describe similar phenotypes and pathology. The disorder has been called corticonigral degeneration with neuronal achromasia,² cortical degeneration with swollen chromatolytic neurons,³ corticobasal ganglionic,⁴ cortical basal ganglionic,⁵ and corticobasal degeneration.⁶

Epidemiology

Corticobasal degeneration typically presents in the sixth to eighth decades of life, with onset of symptoms at mean age 63 years (SD 7.7).⁷ The youngest case, according to pathological confirmation, had onset at age 45 years.⁷ A patient who meets the clinical criteria for this disease with onset at age 28 years has been reported, but confirmation of this diagnosis awaits post-mortem analysis.⁸ Both men and women are affected, with some investigators reporting a predominance of women.^{9–12} Corticobasal degeneration is typically a sporadic disease, although rare familial cases with

pathological confirmation have been described.¹³ Environmental risk factors, such as toxic exposure or infectious agents, have not been implicated in the pathogenesis.

Although corticobasal degeneration is regarded as a rare neurodegenerative disorder, its true incidence and prevalence are unknown. In a recent community-based prevalence study of parkinsonian disorders, not a single case of corticobasal degeneration was identified among 121 628 individuals.¹⁴ Togasaki and Tanner¹⁵ estimated that corticobasal degeneration accounts for 4–6% of parkinsonism, and according to the incidence of Parkinson’s disease, the incidence of corticobasal degeneration would be 0.62–0.92 per 100 000 per year; with a mean survival of 7.9 years, prevalence would be 4.9–7.3 per 100 000.¹⁵

Clinical presentation

Several clinicopathological case series have examined clinical semiology, particularly the typical features at presentation. The data bias the motor presentation to that of atypical parkinsonism, because most of the series have come from movement disorder clinics (case report 1). The diagnostic criteria for corticobasal degeneration were mainly developed from these studies. The disorder may present as a cognitive disorder more than is recognised: such patients are more likely to be referred to behavioural neurology or dementia clinics and are therefore under-reported in most case series.

Initial presentation

Three large studies have addressed the clinical presentation of corticobasal degeneration. Rinne and colleagues⁹ reported five initial presentations in 36 clinically diagnosed patients. The most common presentation (55%) was a “useless arm” (ie, a rigid, dystonic, akinetic, or apraxic arm), gait disorder was the next most common presentation (27%), and the three other presentations—prominent sensory symptoms, isolated speech disturbance, and behavioural disturbance—were rare. Wenning and co-workers⁷ reported 14 patients with pathologically confirmed corticobasal degeneration, in whom limb clumsiness was the most common presenting

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Case report 1

A woman age 69 years presented to a neurologist after 1 year of progressively worsening clumsiness affecting her right hand. She described her right arm, particularly the hand, as feeling "dead", although there was no objective sensory loss on examination. She was noted to have rigidity and bradykinesia affecting the right arm and what was described as a "jerky tremor". A presumptive diagnosis of Parkinson's disease was made, and treatment with levodopa was started. Despite increasing the dose to over 600 mg of levodopa per day, there was no improvement 6 months after presentation. In fact, the patient described a worsening of her right-arm clumsiness and slowness; she reported that her right hand was tending to adopt an increasingly flexed posture, which she found painful. She now described her right arm as "useless". Her husband, who attended with her, described his wife's mood as low, and said that she had become forgetful and muddled in her daily activities. Examination revealed a worsening of the rigidity and bradykinesia previously noted, and a dystonic posture of the right hand with stimulus sensitive myoclonus. Apraxia was difficult to assess in the right arm because of the severity of the dystonia and rigidity, but the left hand was dyspraxic for the miming of tool use and for meaningless gestures. Graphaesthesia was present bilaterally. Reflexes were brisk but symmetrical. Plantar responses were flexor. Her gait had become slow and she tended to drag her right leg. The results of routine blood tests and CSF examination were normal. Standard MRI of the brain was normal. A dopamine transporter single-photon-emission CT scan showed a loss of transporter bilaterally, but worse on the left side. Neuropsychometry revealed deficits in frontal and subcortical areas. A clinical diagnosis of corticobasal degeneration was made. Over the next 2 years her motor symptoms progressed to involve both arms and legs. Progressive memory and mood disturbance were seen. Amantadine was given at a dose of 300 mg per day with no improvement. Botulinum toxin injections were given to release the flexed posture of the right hand with moderate benefit to pain and hygiene. The patient died of pneumonia 3 years after presentation.

symptom (50%), followed by tremor (21%). At the first review by a neurologist, a mean of 3 years after the initial symptoms, unilateral limb rigidity (79%), bradykinesia (71%), ideomotor apraxia (64%), postural instability (45%), unilateral limb dystonia (43%), and dementia (36%) were the most common symptoms.⁷ As follow-up of these patients continued, almost all developed asymmetric, unilateral parkinsonism and gait impairment.⁷ In the largest clinical study of corticobasal degeneration, of 147 patients (only seven of whom had pathologically confirmed disease), all had at least one parkinsonian sign—rigidity, bradykinesia, or tremor/gait disturbance—with 95% having at least two such signs.¹⁶ In addition 93% of the patients had signs of higher cortical dysfunction, such as dyspraxia, cortical sensory loss, dementia, and dysphasia.¹⁶ However, this review was done many years after the presentation of symptoms. Many other presenting symptoms have been reported in smaller case series, including cognitive decline, behavioural changes, gait disorder, speech disorder, myoclonus, sensory disturbance, and depression.¹⁷ Bias in the reported symptomatology (panel 1) is likely because most data are from movement disorder clinics.

Motor symptoms*Parkinsonism and dystonia*

Unilaterality or strong asymmetry is a defining feature of the motor symptoms of corticobasal degeneration. The most common motor feature is asymmetrical parkinsonism affecting a limb, typically an arm. According to the study by

Kompoliti and co-workers,¹⁶ rigidity is the most common manifestation of the parkinsonian syndrome in corticobasal degeneration, followed by bradykinesia, gait disorder, and tremor. The tremor is fast (6–8 Hz), and it differs from the rest or postural tremor typical of Parkinson's disease, which is irregular and jerky.¹⁰ Focal myoclonus, which is commonly stimulus-sensitive, can be superimposed upon the tremor, particularly during advanced stages of the disease, but can also occur as an isolated sign, without associated tremor.¹⁷ Gait disorder is characterised by postural instability and falls, and becomes more prominent as the disease progresses.¹⁷

Asymmetrical limb dystonia is observed in most patients with corticobasal degeneration during progression and can be the presenting symptom.^{7,18,19} Dystonia of the leg is less common than that of the arm, and dystonia of the head, neck, or trunk is rare.¹⁸ The progressive development of a "dystonic clenched fist"¹⁸—a hand held in a flexed, typically fixed, dystonic posture with clenching of the fingers into a fist, closing around the thumb, which is held adducted in the palm—is common. Dystonia is commonly accompanied by pain.¹⁸

Cortical dysfunction

Ideomotor apraxia is common with cortical dysfunction.^{20,21} The clinical complexities presented by apraxia can be difficult to understand when it is combined with bradykinesia, rigidity, and dystonia. Apraxia is bilateral in many patients, and therefore may be more convincingly shown in the limb that is less affected by parkinsonism and

Panel 1. Clinical features of corticobasal degeneration**Motor**

- Limb clumsiness (asymmetric)*
- Bradykinesia/Akinesia (asymmetric)*
- Rigidity (asymmetric)*
- Tremor (action/postural)
- Myoclonus
- Limb dystonia (asymmetric)
- Blepharospasm
- Choreoathetoid movements
- Speech abnormalities
- Gait disorder

Higher cortical functions

- Apraxia (limb more common than orofacial, eyelid-opening)*
- Dementia*
- Alien-limb phenomenon
- Aphasia
- Frontal-lobe-release signs
- Cortical sensory abnormalities

Neuropsychiatric

- Depression, apathy
- Anxiety
- Irritability
- Disinhibition
- Delusions
- Obsessive compulsive disorder

*Most commonly seen in corticobasal degeneration.⁷

dystonia. Apraxia in corticobasal degeneration is typically observed as an impairment in imitation of meaningless or symbolic hand gestures, as well as in the use of real objects.²¹ Patients can have difficulties in tool use, the miming of tool use, and the imitation of mimes of tool use.²¹ Apraxia of the legs may present as difficulty in walking: the foot may seem to stick to the floor as walking is started, or it may drag and cause the patient to trip on uneven surfaces.⁹ Clinically, leg apraxia can be shown by sequences of movements when lying down. Facial apraxia, including impairment of tongue or lip movements, has also been observed in this disorder.²²

The alien-limb phenomenon is common and a sign of cortical dysfunction in corticobasal degeneration. Other signs include grasp, sucking, and rooting reflexes. The alien-limb phenomenon may be defined as a “feeling that one limb is foreign or ‘has a will of its own’, together with observable involuntary motor activity”.²³ Limb levitation alone, which can happen in progressive supranuclear palsy (PSP) and other parkinsonian disorders,²⁴ is not the true alien-limb phenomenon, and can be a source of misdiagnosis. In patients with an alien arm, it is common for their wandering hand to grasp onto (and not release) parts of their body, the bedclothes, adjacent furniture, or even people next to them.²⁵ Many patients are unaware of the movement, and may show signs of neglect of the affected limb, feeling that it is not their own.²⁵ “Intermanual conflict”, where the alien limb interferes with the voluntary activities of the unaffected, or less affected, limb is typical.²⁵ Alien-leg movements may also occur, with the leg rising when the patient is seated.

Cortical sensory loss commonly co-occurs with the alien-limb phenomenon. Typical early cortical sensory symptoms are numbness, tingling, or “deadness” of the affected limb.^{16,17} As corticobasal degeneration progresses, impaired two-point discrimination, graphaesthesia, and stereognosis with intact primary sensory modalities are common.^{16,17}

Cognition and dementia

Although cognitive impairment was thought to be a rare or late-occurring manifestation of corticobasal degeneration¹⁹ more recent studies showed that cognitive decline is a common feature of the disorder;²⁶ furthermore, dementia may be the presenting feature.²⁷ The diagnostic research criteria reflect these changes: in the 1994 criteria, early dementia was an exclusion criterion for diagnosis;²⁸ in the proposed 2003 criteria, certain cognitive impairments support a diagnosis.²⁹ Cognitive decline or dementia are probably the commonest features leading to misdiagnosis of corticobasal degeneration, perhaps because patients are more likely to be seen outside of specialist movement disorder clinics.³⁰

The variety of cognitive impairment in corticobasal degeneration has been the subject of a detailed review by Graham and colleagues.²⁶ Impairment of spoken-language production, especially such that it is non-fluent, is a very common feature of this disease. In Graham and colleagues²⁶ analysis of 42 studies (399 patients), 34% of all reported patients with corticobasal degeneration and 44% with

pathological confirmation had aphasia. Frontal executive impairment is also common; this was found in all 21 patients Dubois and co-workers³¹ tested with the Frontal Assessment Battery. Consistent with pathological evidence of parietal-lobe involvement in corticobasal degeneration, calculation and visuospatial skills are also commonly impaired. By contrast, probably reflecting the relative lack of temporal-lobe pathology, semantic memory may be spared, and episodic memory impairment is generally less prominent than in patients with Alzheimer's disease.²⁶ In view of this range of neuropsychological impairments, a formal cognitive assessment may be useful in the clinical assessment of a patient with suspected corticobasal degeneration.²⁶

A particularly difficult diagnostic group are those patients with corticobasal degeneration who present solely with cognitive decline or frank dementia. Some of these patients will go on to develop a movement disorder,³² whereas, in others, cognitive impairment may remain the sole manifestation of the disease.³³ The commonest cognitive presentations are a prominent speech-production impairment resembling the progressive non-fluent aphasic subtype of frontotemporal lobar degeneration (FTLD),^{34,35} or a prominent progressive behavioural change resembling the frontotemporal dementia subtype.³⁶ As in FTLD, these subtypes commonly overlap (case report 2). Although the nosology of FTLD³⁷ or “Pick's complex”³⁸ remains controversial,²⁶ corticobasal degeneration should be included in the differential diagnosis of patients presenting with a frontal dementia, particularly with non-fluent speech production, alongside other tau (eg, frontotemporal dementia and parkinsonism linked to chromosome 17, Pick's disease, and PSP) and non-tau (eg, ubiquitin-positive, tau-negative inclusion body disease) pathologies.

Psychiatric features

In addition to dementia, common psychological complaints include depression (73%), apathy (40%), irritability (20%),

Case report 2

A right-handed, 65-year-old man with a 3 year history of difficulties in understanding others and making himself understood presented to a neurologist. The initial symptom had been difficulty in expressing individual words. His condition was slowly progressive, but he was able to drive safely, navigate new and familiar routes, and operate household devices. Because of communication difficulties, he had given up his hobby as a sports referee. He had become slightly more rigid in his routines but there was no evidence of disinhibition or of a change in feeding behaviour. There was no family history of neurological disease and no relevant past medical history. Neurological examination was normal except for a profound speech production problem, orofacial dyspraxia, and frontal-lobe dysfunction with perseveration, confirmed on formal neuropsychological testing. There was no limb apraxia, myoclonus, or alien-limb phenomena. A year later, spoken language had deteriorated to rambling speech, of which only a few words were intelligible. Further evidence of frontal-lobe dysfunction with utilisation behaviour was clear. Again there was no evidence of asymmetric limb apraxia or myoclonus. MRI showed moderate asymmetric frontotemporal atrophy, greater on the left than on the right; results of CSF and blood tests were normal. A diagnosis of probable Pick's disease was made. He had a stroke later the same year, and died age 67 years. A post mortem confirmed the diagnosis of corticobasal degeneration.

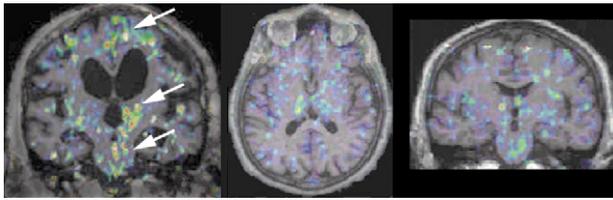


Figure 1. PET scans showing microglial activation in a patient with corticobasal degeneration compared with a healthy person. Left: patient age 67 years who has had the disease for 5 years and has a flexed right arm, a dyspraxic left hand, and myoclonic jerks. Arrows (top to bottom) show increased activation in the left cortex, thalamus, and pons respectively. Middle and Right: healthy 59-year-old person with low constitutive binding in the thalamus and pons. All images are calibrated for binding potential values. Picture supplied by A Gerhard and D Brooks, MRC Clinical Sciences Centre and Division of Neuroscience, Faculty of Medicine, Imperial College, London, UK.

and agitation (20%).³⁹ Other psychological features that have been reported include anxiety, disinhibition, and delusions.³⁹ Obsessive-compulsive symptoms, including recurrent thoughts, repetitive acts, checking behaviours, and perfectionism are similarly described.³⁹ An overlap between these symptoms and the frontal cognitive impairment seen in corticobasal degeneration is likely.

Other clinical signs

Eye movements may help with differential diagnosis. The eye movement abnormality most strongly associated with corticobasal degeneration is difficulty and delay in initiating saccades; once saccades are initiated they are of normal velocity and range.⁴⁰ The maximum abnormality is typically identified in horizontal saccades, whereas vertical saccades can be preserved—a useful point of differentiation from PSP. This is not always the case, however, and patients with pathologically proven corticobasal degeneration have been reported with an early and severe vertical supranuclear gaze palsy.⁴¹

A mixture of other clinical signs have been reported, including a Balint's-like syndrome,⁴² pyramidal signs, cerebellar signs, severe pain, and dysphagia.¹⁸

Differential diagnosis: the “corticobasal degeneration-lookalike” syndromes

Clinical diagnosis can be difficult because of overlap with other neurodegenerative disorders. Despite a high specificity of clinical diagnosis (nearly 100%), sensitivity is only about 35% at presentation, rising to about 48% at the last visit.⁹ Of all the disorders that may be confused with corticobasal degeneration, perhaps the most difficult to differentiate is PSP. Although patients with PSP typically present with prominent axial rigidity, postural instability, and abnormal vertical eye movements, atypical manifestations of PSP are many and include asymmetric onset, mild oculomotor impairment, focal dystonia, and involuntary limb levitation resembling the alien-limb phenomenon.^{43,44} The underlying pathological similarities between PSP and corticobasal degeneration (eg, tau pathology), may explain their clinical similarity.

Because corticobasal degeneration can predominantly present as dementia, there may be diagnostic confusion with

other dementing diseases. The substantial overlap between corticobasal degeneration, progressive nonfluent aphasia, and frontotemporal dementia may lead to particular diagnostic difficulties.³⁵ Alzheimer's disease,^{45,46} sometimes in combination with Lewy-body pathology,⁴⁷ rarely presents with motor features suggestive of a corticobasal-degeneration-like phenotype. Other syndromes that may be similar to corticobasal degeneration include Parkinson's disease, multiple-system atrophy, Wilson's disease, progressive subcortical gliosis, rigid-akinetic type Huntington's disease, atypical Pick's disease, parkinsonism-dementia-amyotrophic-lateral-sclerosis complex prion-related disease, sudanophilic leukodystrophy, and neurofilament inclusion disease.^{48–50}

Investigations

Imaging and electrophysiology

Results of routine laboratory studies of blood, urine, and CSF are normal in patients with corticobasal degeneration. CT and MRI scans of the brain tend to be 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.^{51,52}

Electroencephalograms may be normal at first, but may later show asymmetric slowing that is maximum over the hemisphere contralateral to the more affected limbs. Nerve-conduction studies, electromyography, and evoked potential studies have not shown any consistent patterns of impairment.^{53,54}

Functional imaging studies may be of use in the differential diagnosis of patients with suspected corticobasal degeneration. Dopamine transporter single-photon-emission CT scans are commonly abnormal in these patients,⁵⁵ and can help to differentiate them from those with Alzheimer's and Pick's diseases (in whom this scan is typically normal) early in the course of the disease.⁵⁶ This type of scan does not help to differentiate other parkinsonian syndromes, such as PSP or idiopathic Parkinson's disease.⁵⁵ Studies of patients with clinically diagnosed corticobasal degeneration have shown asymmetric reductions in resting levels of glucose metabolism and blood flow in the posterior frontal, inferior parietal, and superior temporal regions, thalamus, and striatum measured by PET or single-photon-emission CT scanning.⁵⁷ Because such a pattern is not typically seen in idiopathic Parkinson's disease or PSP, these scans might be helpful.⁵⁷ New forms of imaging show some promise: microglial activation PET scans with the PK11195 ligand have shown asymmetric basal ganglia and cortical activation in corticobasal degeneration (figure 1).^{58,59} Whether this pattern of activation will discriminate between patients with this disorder and those with other parkinsonian disorders awaits further study.

Histopathology

Given the uncertainty of clinical criteria for the diagnosis of corticobasal degeneration, neuropathological investigation is needed to make a definitive diagnosis. Severe focal cortical

atrophy is centred on the peri-Rolandic posterior frontal and parietal cortex, with lesser involvement of adjacent cortex and relative sparing of the temporal and occipital regions.⁶⁰ The motor and sensory areas of the cerebral cortex are most severely affected, and there is secondary degeneration of the corticospinal tracts.⁶⁰ The cortical atrophy tends to be asymmetric—most severe on the side contralateral to the limb most affected.⁶⁰ In the dementing or aphasic presentation, however, a more symmetric and more severe involvement of the frontal and temporal lobes may be present. In the cortical regions affected, the normal cortical architecture is destroyed, the definition of the cortical layers is lost, and there is intense fibrillary gliosis. There is substantial atrophy and cell loss accompanied by gliosis in the lateral two-thirds of the substantia nigra with loss of pigmented cells.^{1,6}

Large pale neurons—“neuronal achromasia” in the original description by Rebeiz and co-workers¹—are characteristic of the pathology. The cortical neurons affected are medium to large pyramidal cells, which are most prominent in the third, fifth, and sixth laminae of the cortex. The nucleus of affected neurons is eccentrically located, and Nissl substance is not detected within the neurons, distinguishing the degeneration from that seen in central chromatolysis.^{1,2} The cytoplasm stains positively for phosphorylated neurofilaments and beta crystalline and variably with antibodies to ubiquitin and tau (figure 2).^{6,61,62} The presence of these ballooned neurons was thought to be a unique feature of corticobasal degeneration and Pick's disease; however, they are also, more rarely, seen in PSP, Alzheimer's disease, frontotemporal dementia, and Creutzfeldt-Jakob disease. Thus, the distribution and number of ballooned neurons at different sites is crucial for diagnosis, as is the ultrastructural pattern of neurofilaments.⁶⁰ Others have highlighted the importance of astrocytic plaques in the pathological diagnosis of corticobasal degeneration.⁶³

Molecular pathology

Corticobasal degeneration is one of several neurodegenerative diseases characterised by accumulation of hyperphosphorylated tau, forming abnormal filamentous inclusions in neurons and glia (panel 2).⁶⁴ The *tau* gene is located on chromosome 17 and has 13 exons. Both corticobasal degeneration and PSP show a similar pattern of *tau* expression on electrophoresis, with 64 and 68 kDa doublets, however, corticobasal inclusions typically lack exon 3 sequences.⁶⁵ In corticobasal degeneration tau forms paired helical filaments.⁶² Thus, the lobar and basal ganglia tauopathy in this disease is distinct, with selective aggregation of four-repeat tau, which has characteristic antigenic and ultrastructural features.^{63,66}

The *tau* haplotype H1 has been associated with PSP, which has led to similar studies in corticobasal degeneration; Di Maria and co-workers⁶⁷ found the same association in cases with a clinical diagnosis and Houlden and colleagues⁶⁸ found this association in 57 pathologically confirmed cases. The finding that the H1 haplotype is associated with both corticobasal degeneration and PSP has led to the hypothesis

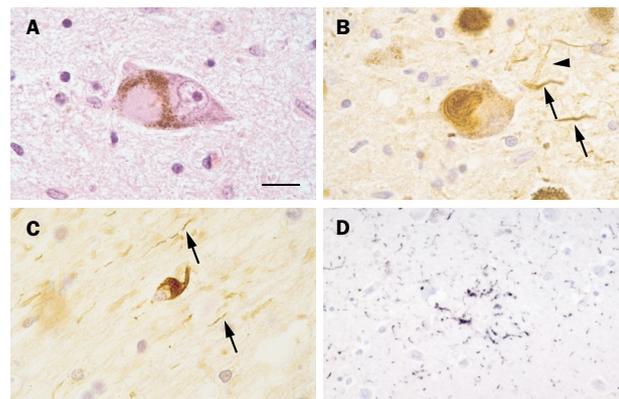


Figure 2. Cortical and striatal tau-positive neuronal and glial inclusions. Pigmented neurons in the substantia nigra have globose neurofibrillary tangles that displace the neuromelanin granules (A). Immunohistochemical staining for tau highlights neurofibrillary tangles and neuropil threads, shown with arrows (B). In white matter, structures such as the internal capsule coiled bodies are present in oligodendroglia and there are many neuropil threads, shown with arrows (C). Astrocytic plaques are conspicuous in the putamen (D). Bar represents 15 μm in A–C and 30 μm in D. Pictures courtesy of J Holton and T Revesz, Queen Square Brain Bank, Department of Molecular Neuroscience and Division of Neuropathology, Institute of Neurology, University College London, London, UK.

that abnormalities of *tau* on chromosome 17 may cause both diseases. Interestingly, a similar phenotype to that of corticobasal degeneration⁶² has been described in some families with frontotemporal dementia with parkinsonism linked to chromosome-17—with mutations located in exon 10 of *tau* or in the 59 exon splice site of exon 10—although, typically sporadic cases do not have mutations of the *tau* gene.⁶² The clinical importance of this molecular link between PSP and corticobasal degeneration needs to be established, and whether they are two ends of a spectrum of one disorder or two different disorders with a similar genetic predisposition is unknown.²⁷

Neuropathological criteria have been detailed and validated for the diagnosis of corticobasal degeneration (panel 3)⁶⁰ and advance the diagnosis of corticobasal degeneration at post mortem. Over time the criteria should help establish the true variety and frequency of clinical phenotypes associated with this pathology. In turn the diagnostic criteria will be refined to allow more accurate diagnosis of patients.

Panel 2. Tauopathies

PSP
Corticobasal degeneration
Frontotemporal dementia parkinsonism linked to chromosome 17
Postencephalitic parkinsonism (encephalitis lethargica)
Post-traumatic parkinsonism (including dementia pugilistica)
Parkinson–dementia complex of Guam
Alzheimer's disease
Niemann–Pick type C
Subacute sclerosing panencephalitis

Adapted from Morris and colleagues⁶⁴

Panel 3. Neuropathological criteria for corticobasal degeneration**Core features**

Focal cortical neuronal loss
 Substantia nigra neuronal loss
 Cortical and striatal Gallyas/tau-positive neuronal and glial lesions, especially astrocytic plaques and threads, in both white and grey matter

Supportive features

Cortical atrophy, commonly with superficial spongiosis
 Ballooned neurons, typically many in atrophic cortices
 Tau-positive oligodendroglial coiled bodies

Adapted from Dickson and colleagues⁹

Clinical diagnostic criteria

Given the clinical heterogeneity of corticobasal degeneration and the overlap of symptoms with other neurodegenerative diseases, there have been various attempts to create diagnostic criteria for clinical and research use. The first such criteria, outlined by Riley and colleagues⁵ comprised unilateral onset and asymmetric course, insidious onset with gradual progression, and clinical signs reflecting dysfunction in both cerebral cortex and basal ganglia. These criteria are broad, and would be likely to include many patients with other neurodegenerative disorders. Lang and co-workers²⁸ have developed formal diagnostic criteria (panel 4), mostly for use in research (eg, recruiting appropriate participants into clinical trials). Notably, these inclusion criteria focus on the motor presentations and early dementia is a specific exclusion criterion. Lang and co-workers accept that this particular criterion will exclude some patients, but may be necessary for sufficient specificity of diagnosis. Since the development of these criteria, alternative diagnostic criteria have been proposed with “core features” focused on the motor symptomatology but including “supportive investigations” of specific neuropsychological impairment, and structural and functional imaging abnormalities (panel 5).²⁹ These criteria are yet to be tested for accuracy in patients with pathologically confirmed corticobasal degeneration, but are a shift towards a more inclusive set of guidelines, with the incorporation of cognitive dysfunction and advances in the functional and structural imaging of this disease.

Treatment

There is no curative treatment for corticobasal degeneration.¹⁶ Management of symptoms and support can help patients with this disease.

Motor symptoms

Levodopa and other dopaminergic drugs may provide limited benefit to some patients. Although one study reported improvement in 24% of clinically diagnosed patients that received levodopa,¹⁶ other studies have not found a high level of levodopa responsiveness.¹⁸ Levodopa-induced dyskinesias can occur, even in the absence of objective clinical benefit.⁶⁹ Other dopaminergic drugs, such as dopamine agonists and selegiline hydrochloride, tend to provide less clinical improvement and have more side-effects

than levodopa.¹⁶ In one clinically diagnosed case, amantadine hydrochloride has been reported to improve ideomotor apraxia (eg, the ability to dress).⁷⁰

Baclofen alone or in combination with an anticholinergic can help to reduce rigidity but can produce unwanted side-effects.^{16,18} Clonazepam can be helpful with regard to myoclonus and tremor.¹⁶ Many other drugs, including propranolol, dantrolene sodium, and anticonvulsants, have been tried, generally without notable benefit.¹⁶ Botulinum toxin injections into dystonic limb muscles provide symptomatic relief of pain and prevent skin damage, particularly for “dystonic clenched fist”.^{16,18,71}

Cortical dysfunction

The basal forebrain cholinergic neurons are not particularly involved in the disease process,⁶⁰ suggesting that central cholinergic drugs, such as cholinesterase inhibitors, are not helpful in treating the dementia, although no formal trials have been done. One study of patients with perseveration as part of their dementia has reported benefit from treatment with bromocriptine mesilate.⁷² Although no formal trials have been done in patients with corticobasal degeneration, neuropsychiatric symptoms such as depression are probably best treated with serotonin reuptake inhibitors.³⁹

Other symptoms

Dysphagia is an important late-presenting symptom. Awareness and investigation of dysphagia is important, because aspiration is a cause of morbidity and mortality. Dietary modification and nasogastric and percutaneous endoscopic feeding may be necessary. Constipation should be treated with stool softeners, increased fluid intake, food rich in fibre, and laxatives. Urinary urgency and frequency may be treated with anticholinergic drugs, although side-effects can limit this. Physiotherapy and occupational therapy can be of benefit, although apraxia may limit the abilities of some patients to respond to certain physical therapeutic interventions. Falls can be an important cause of morbidity and mortality, and prompt provision of appropriate walking aids or a wheelchair is

Panel 4. Diagnostic criteria for corticobasal degeneration²⁸**Inclusion criteria (one of A or B)**

Rigidity (easily detectable without reinforcement) and one cortical sign:
 apraxia (more than simple use of limb as object; absence of cognitive or motor deficit sufficient to explain disturbance)
 cortical sensory loss (preserved primary sensation, asymmetric)
 alien-limb phenomenon (more than simple levitation)
 Asymmetric rigidity, dystonia (focal in limb; present at rest at onset), and focal reflex myoclonus (spreads beyond stimulated digits)

Exclusion criteria

Early dementia (will exclude some patients with corticobasal degeneration)
 Early vertical gaze palsy
 Rest tremor
 Severe autonomic disturbances
 Sustained responsiveness to levodopa
 Lesions on imaging studies indicate another pathological process

Panel 5. Proposed criteria for the diagnosis of corticobasal degeneration

Core features

Insidious onset and progressive course
 No identifiable cause (eg, tumour, infarct)
 Cortical dysfunction includes at least one of the following:
 focal or asymmetric ideomotor apraxia
 alien-limb phenomena
 cortical sensory loss
 visual or sensory hemineglect
 constructional apraxia
 focal or asymmetric myoclonus
 apraxia of speech or nonfluent aphasia

Extrapyramidal dysfunction as reflected by one of the following:

focal or asymmetric appendicular rigidity lacking prominent and sustained l-dopa response
 focal or asymmetric appendicular dystonia

Supportive investigations

Variable degrees of focal or lateralised cognitive dysfunction, with relative preservation of learning and memory on neuropsychometric testing
 Focal or asymmetric atrophy on CT or MRI imaging, typically in perirhinal cortex
 Focal or asymmetric hypoperfusion on SPECT or PET, typically maximal in parietofrontal cortex with or without basal ganglia involvement
 Adapted from Boeve and colleagues²⁹

Search strategy and selection criteria

References for this review were identified from searches of MEDLINE from 1980 to July 2004 with the terms "CBD", "corticobasal degeneration", "corticobasal ganglionic degeneration", and "corticodentatonigral degeneration". References were also identified from relevant articles and from the authors' files.

of specialised functional imaging methods in differential diagnosis, post-mortem neuropathology is the only definitive method of diagnosis. Current diagnostic criteria are likely to be biased towards "atypical parkinsonism" and may exclude patients with a mainly cognitive presentation of the disease. Available treatments address symptoms, and are generally only moderately or poorly effective. Future work is likely to be directed towards improved clinical and imaging diagnostic criteria allowing delineation of a well-defined cohort of patients for entry into clinical trials of symptomatic and neuroprotective, as well as ongoing work to investigate the underlying pathological hallmarks of the disorder.

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Authors' contributions

All authors contributed equally to this work.

Conflict of interest

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helpful. Caring for a family member can be a difficult and demanding task, and therefore appropriate support for carers is essential.

Conclusion

There have been incremental advances in the understanding of the genetics, cellular pathology, and clinical features of corticobasal degeneration. However, clinical diagnosis of this heterogeneous disorder is difficult, and despite the use

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