Review article

VISUAL SIGNS AND SYMPTOMS OF CORTICOBASAL DEGENERATION

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Abbreviated Title: Vision in corticobasal degeneration

Summary

Corticobasal degeneration is a rare, progressive neurodegenerative disease and a member of the ‘parkinsonian’ group of disorders which also includes Parkinson’s disease, progressive supranuclear palsy, dementia with Lewy bodies, and multiple system atrophy. The most common initial symptom is limb clumsiness, usually affecting one side of the body, with or without accompanying rigidity or tremor. Subsequently, the disease affects gait and there is a slow progression to influence ipsilateral arms and legs. Apraxia and dementia are the most common cortical signs. Corticobasal degeneration can be difficult to distinguish from other parkinsonian syndromes, but if ocular signs and symptoms are present they may aid clinical diagnosis. Typical ocular features include increased latency of saccadic eye movements ipsilateral to the side exhibiting apraxia, impaired smooth pursuit movements, and visuo-spatial dysfunction especially involving spatial rather than object-based tasks. Less typical features include reduction in saccadic velocity, vertical gaze palsy, visual hallucinations, sleep disturbance, and an impaired electroretinogram. Aspects of primary vision such as visual acuity and colour vision are usually unaffected. Management of the condition to deal with problems of walking, movement, daily tasks, and speech problems is an important aspect of the disease.

Key Words: Tauopathy, Parkinsonian syndrome, Saccadic eye movement, Visuo-spatial function

Introduction

Corticobasal degeneration (CBD) is a rare, progressive neurodegenerative disease affecting approximately 4.9-7.3/100,000 of the population.[1] CBD largely affects individuals older than 60 years of age and death usually occurs within eight years of disease onset. The original description of the disease is based on three cases described as 'corticodentatonigral degeneration achromasia'.[2] The disorder has also been referred to as 'corticoganglionic degeneration'[3] but CBD remains the most popular descriptive term. Patients with a combination of clinical symptoms suggestive of the disorder are often referred to as having 'corticobasal syndrome' (CBS), while CBD is used strictly to describe cases verified at post-mortem.[4]

Clinical diagnosis of CBD can be difficult as symptoms are variable and often resemble those of other types of neurodegenerative disorder. First, CBD is classified as a subtype of frontotemporal lobar degeneration (FTLD)[5], the second most frequent form of cortical dementia of early-onset after Alzheimer's disease (AD).[6] Second, CBD is characterized by a cellular pathology consisting of abnormal cellular aggregations of the microtubule-associated protein (MAP) tau, and in this respect is similar to AD[7] and progressive supranuclear palsy (PSP).[8] Third, CBD is included within the 'parkinsonian' group of disorders, which includes Parkinson's disease (PD)[9], PSP[8], dementia with Lewy bodies (DLB)[10], and multiple system atrophy (MSA).[11]

Visual signs and symptoms are frequently present in parkinsonian syndromes.[8-11] CBD can be difficult to distinguish from the other parkinsonian syndromes, but if ocular signs and symptoms occur they can aid clinical diagnosis. Hence, this review describes: (1) the major clinical and pathological features of CBD, (2) the visual signs and symptoms that have been identified, (3) the visual features which may help to distinguish CBD from other parkinsonian disorders, and (4) management of the disease.

Clinical features

The onset of CBD is often sudden, patients exhibiting problems affecting cortical processing and motor function. The major clinical features include cortical signs such as apraxia and dementia[12], parkinsonism, palsy, and myoclonus.[13] The most common initial symptom is limb clumsiness affecting one side of the body, initially with or without accompanying rigidity or tremor.[12,14,15] Subsequently, the disease spreads to affect gait and there is a slow progression to influence ipsilateral arms and legs.[14]

The motor symptoms of CBD include parkinsonism, 'alien hand syndrome', and apraxia.[4] The parkinsonism usually affects the extremities of the limb, is frequently asymmetric, and characterized by rigidity and bradykinesia. Alien hand syndrome is present in approximately 60% of affected individuals and is a failure to control the movement of a hand accompanied by a sensation that the hand is 'foreign' to the patient.[16] The affected hand may also try to avoid specific external stimuli such as heat, cold, or touch and may exhibit an itching or prickling sensation. By contrast, the apraxia is characterized by an inability to repeat a specific movement of the hands and arms or an inability to carry out such a movement on command. 'Limb-kinetic' apraxia may also occur and is a dysfunction of fine movement control involving the hands.[16] Myoclonus has also been observed in CBD and may result from the degeneration of an enhanced 'long-loop reflex' pathway[17], rather than the classic 'cortical reflex' myoclonus pathway.[18]

Aphasia is present in some CBD patients and may involve disconnected speech and the omission of critical words.[1] As the disease progresses, the patient may lose the ability to speak completely. These problems may be accompanied by irritability, depression, and cortical dementia which can result in confusion with AD.[19] Neuropsychological problems may also be present and include deterioration of 'global' function, frontal lobe signs ('dysexecutive syndrome'), and learning difficulties.[20]

Neuropathology

Gross features

Neuropathologically, CBD is characterised by a progressive and asymmetric cortical atrophy affecting the anterior cerebral cortex[21], the fronto-parietal region[17], and the superior temporal cortex.[17] There is also atrophy of the basal ganglia, including the caudate nucleus[22] and substantia nigra.[23] Fig 1 illustrates a coronal section of the striatum and adjacent regions from a pathologically confirmed case of CBD showing enlarged lateral ventricles and atrophy of the caudate nucleus head, while the internal capsule, insula, putamen, and globus pallidus appear more normal. A summary of presenting features, motor symptoms, and brain regions affected in CBD compared with closely-related disorders such as PSP, PD, and AD is shown in Table 1.

Histopathology

There is a widespread neuronal and glial histopathology in CBD (Fig 2) affecting several different types of cell.[24] Abnormalities of neurons include enlarged neuronal cell bodies[25], thread-like dystrophic neurites[26], and abnormal cellular protein aggregates, viz., 'neuronal cytoplasmic inclusions' (NCI).[17] Pathology may also affect glial cells resulting in oligodendroglial inclusions[27] and degeneration of astrocytes and their processes ('astrocytic plaques').[28]

The typical distribution of the pathology in CBD is shown in Fig 3. First, pathology is frequently present in posterior frontal lobe anterior to the precentral gyrus but may be less severe in primary motor cortex.[21] Second, NCI are frequent in temporal lobe, including the superior temporal gyrus and parahippocampal gyrus, and in the cornu ammonis sectors of the hippocampus, less abundant in frontal and parietal cortex, and only present at low density in the dentate gyrus.[29] Third, NCI have been observed in association visual cortex (areas V2, V3).[30] Fourth, enlarged neurons occur in a variety of regions including frontal cortex[31], cingulate gyrus, superior frontal cortex, motor cortex, brainstem tegmentum, basal ganglia, thalamus, insula, claustrum, and amygdala.[27,31]

Molecular pathology

The pathology of CBD can be revealed using a variety of histological stains and

immunohistochemical procedures but the most sensitive are antibodies raised against the microtubule protein tau.[32] Tau is encoded by the tau gene on chromosome 17, alternative splicing of exons 2, 3, and 10 resulting in six possible isoforms. Hence, tau resulting from encoding exon 10 is known as 4-repeat (4R) tau while tau lacking exon 10 is referred as 3-repeat (3R) tau.[33] CBD is characterized by 4R tau similar to that of PSP, and distinct from those tauopathies that consist largely of either 3R tau alone, such as Pick's disease, or a mixture of 3R and 4R tau as in AD.[34] Electron microscopy reveals that the tau-immunoreactive NCI are composed of paired helically-wound filaments, those of CBD being wider than in AD and with a longer periodicity.[35] Inclusions can also be found in oligodendrocytes in cortical white matter.[36] These inclusions are often immunoreactive to tau, ubiquitin, heat shock protein, and alpha-B-crystallin. Neuropil threads may also occur in the white matter of the spinal cord especially the anterior funiculus.[23] β-amyloid (Aβ) protein deposits have also been observed in some cases of CBD resembling those found in AD.[15,37]

Neuroimaging

Magnetic resonance imaging (MRI) studies reveal the typical asymmetric cortical atrophy of CBD affecting posterior parietal and frontal regions together with atrophy of the corpus callosum.[38] In addition, functional MRI (fMRI), utilizing a simple finger tapping task, has revealed lower levels of activity in parietal cortex, motor cortex, and supplementary motor cortex in CBD.[38] Hypoperfusion in posterior frontal cortex and parietal cortex as well as abnormalities in thalamus, temporal cortex, basal ganglia, and pontocerebellar fibres has also been demonstrated using single photon emission computed tomography (SPECT).[39] Consistent with post-mortem findings, fDOPA positron emission tomography (PET) reveals diminished dopamine uptake in the striatum. In addition, hypometabolism in the thalamus has been reported.[40] Regional cerebral blood flow (rCBF) PET studies indicate that the clinically affected hemisphere has significantly reduced flow in posterior frontal and parietal cortices as well as in the thalamus and basal ganglia, while temporal and occipital lobes are essentially normal.[22] In a particularly significant study, SPECT was used in association with mapping of anatomical areas to reveal hypoperfusion in visual areas V1 and V2 in CBD.[41]

Diagnosis

Clinical and pathological diagnosis of CBS/CBD can be difficult as there is no specific clinical phenotype characteristic of the disease[42] and the neuropathology of CBD overlaps with that of AD, other forms of FTLD[43], the parkinsonian syndromes, and tauopathies.[19] Diagnosis is further complicated by the presence of possible subtypes of CBD including those characterized by selective atrophy of: (1) fronto-parietal, (2) exclusively frontal, and (3) superior temporal regions.[17] Some neuropsychiatric features of CBD may be useful in diagnosis. Hence, CBD subjects are significantly better than those with AD on tests of immediate and delayed recall of verbal material while AD subjects are better on tests of praxis, finger tapping speed, and motor tasks generally.[44] In addition, CBD subjects exhibit a wide range of cognitive and behavioural deficits which include in executive function and memory with non-specific language and visual spatial deficits whereas PSP subjects show apathy and impulsivity as consistent features.[45] CBD is currently diagnosed using criteria recommended by the National Institute of Health (NIH) Office of Rare Diseases.[42] A specific clinical phenotype is not required as diverse clinical symptoms may be present. Pathological diagnosis is based on the presence of: (1) tau-immunoreactive NCI together with inclusions in oligodendrocytes, and the presence of astrocytic plaques, (2) NCI in the white and gray matter of cortical regions and striatum, and (3) neuronal loss in focal cortical areas and in the substantia nigra.

Causes

No specific cause of CBD has yet been established and few risk factors have been identified. Hence, the disease does not appear to be associated with stress, overwork, pregnancy, smoking, alcohol, diet, or social class. In addition, there is no evidence that it is caused by a virus or other infectious agent. Approximately 32% cases have a family history of the disease,[46] familial cases being equally distributed between those exhibiting a primarily parkinsonian-type syndrome and those with cortical dementia. Mutations affecting the alternate-spliced exon 10 or the 5’ regulatory region of the tau gene can result in the typical tau-reactive inclusions characteristic of CBD.[47] In

addition, a rare mutation of the tau gene has been reported in a single case of CBD.[48] Research also suggests a possible association between CBD and mutations of the progranulin[49], and fused in sarcoma[50] genes, which have also been implicated in FTLD.[5]

Treatment

There are no medications that can prevent or slow the development of CBD but various treatments are used to control symptoms. Hence, the parkinsonism is treated with levodopa/carbidopa, and rigidity specifically with baclofen.[51] Levodopa/carbidopa are usually less effective in CBD than in PD, however, but there may be some short-term improvement in rigidity and muscle stiffness. Limb dystonia is treated with botulinum toxin and myclonus with clonazepam and levetiracetam.[52] Memantine, a N-methyl-D-aspartate antagonist, and originally designed to reduce abnormal brain activity in AD, may have a similar affect in CBD.[52] Nevertheless, effectiveness of this treatment is controversial and can result in side effects such as headache, dizziness, and shortness of breath. Visual side effects have been observed in association with Levodopa/carbidopa (mydriasis, miosis, blepharospasm, eyelid ptosis, diplopia, and reduced vision), baclofen (diplopia and visual hallucinations), levetiracetam (diplopia), and memantine (blurred vision, yellowing of eyes and skin).

Visual signs and symptoms

The major visual signs and symptoms described to date in CBD are summarized in Table 2. Caution is required in interpreting these data as: (1) vision has been studied less frequently in CBD than in other parkinsonian disorders[8-11], (2) studies rely on a clinical diagnosis of CBS which can be difficult[42], and (3) CBD is rare and therefore sample sizes in clinical studies often limited.

Primary vision

There are few data concerning changes in primary vision in CBD such as visual acuity. Nevertheless, patients with a parkinsonian syndrome often complain of poor

vision as the disease progresses, and such changes could be present in CBD.[8-11] Nevertheless, in CBD patients, in which difficulties involving visuospatial tasks or in reading ability have been reported, the patients denied that they had a significant visual loss.[53] Photophobia appears to be significantly less frequent in CBD than in PSP.[54]

Visual fields

There have been few studies to date of visual field defects in any parkinsonian syndrome.[8-11] However, in a single case of a lateralized cortical-subcortical dementia, CBD being the most likely diagnosis, there was left visual field inattention consistent with right hemisphere pathology.[55] In addition, in six patients exhibiting posterior cortical atrophy (PCA), one of whom was diagnosed as CBD, a homonymous hemanopia, an inability to perceive more than a single object at a time (simultanagnosia), 'Balint's syndrome', visual agnosia, facial recognition problems, and hemispatial neglect were present.[56] Hence, an isolateral homonymous hemianopia may be suggestive of a diagnosis of PCA and therefore, of possible CBD.[56] In addition, the highly lateralized pathology characteristic of CBD suggests that hemianopias could be more common in this disorder than in other parkinsonian syndromes.

Eyelids and associated structures

Apraxia of eyelid opening has been observed in CBD and results from defective coordination between the action of the orbicularis oculi and levator palpebrae muscles.[57] Eyelid reflexes are impaired in several parkinsonian syndromes, especially in PSP[8], and includes the 'acoustic blink reflex' and 'acoustic startle reflex', responses to a sudden and unexpected sound by a brief closing of the eye. In a single case diagnosed as severe CBD, the blink reflex was completely absent.[58] Blepharospasm is a common symptom in parkinsonian syndromes, especially in PSP and MSA, and is also present in CBD.[59,60] Prominent blepharospasm in untreated patients with parkinsonism may suggest CBD.[61]

Eye movement

One of the most consistent eye movement problems reported in CBD is an increase in saccadic latency, i.e., time from appearance of a target to the beginning of the saccadic response, as measured by electro-oculography (EOG).[62,63] In a study which included six CBD and three atypical CBD cases, increased latency was ipsilateral to the side exhibiting the most significant apraxia.[62] In addition, in a study of 10 CBD cases, increased latency was correlated with the degree of apraxia.[64] In more atypical cases of CBD, vertical saccades and an early slowing of horizontal saccades have been reported but there was no increase in latency or early square-wave jerks.[62] Vertical saccade paralysis has been rarely observed in PD and CBD but is present in the majority of patients with PSP.[64] By contrast, normal antisaccadic error rates (where eye movements are deliberately made in a direction opposite to the visual stimulus) have been recorded in CBD, a feature also demonstrated in PD[65], but error rates are often increased in PSP.[64] However, in a study of 15 cases of CBS, patients were impaired on antisaccadic tasks and were not able to spontaneously self-correct antisaccadic errors as well as controls.[66] In addition, in more complex 'mixed' tasks, an increase in prosaccade and antisaccade error rates was reported in CBD.[65]

In one of the largest visual studies of CBD to date, which involved 36 well-characterized patients, smooth pursuit movements were commonly affected, a significant number of patients presenting with 'jerky' smooth pursuit movements, and in a small number of these patients, the range of movement was also restricted.[14] Decreased gain of smooth pursuit movements has also been observed in CBD.[64] Square-wave jerks have been reported in CBD.[14,67,68] while abnormal optokinetic nystagmus also appears to be common.[53,69]

Vestibulo-ocular reflex (VOR)

The vestibulo-ocular reflex (VOR) is a reflex eye movement that stabilizes images on the retina during movements of the head. The 'gain' of the VOR is the ratio of the change in eye angle to head angle during a head turn. If the gain is impaired (ratio not equal to unity), head movements result in image motion on the retina and blurred

vision. The gain of the VOR in the dark may be cancelled by fixation. Both MSA and PSP patients show this cancellation compared with control cases and PD[70], a response which could be related to cerebellar dysfunction. However, in CBD, in which there is less cerebellar pathology, there is little evidence for an effect on VOR.

Electroencephalography (EEG)

A slowing of general background activity and the appearance of focal slow waves have been recorded in CBD.[71] Intermittent delta activity has also been recorded in both CBD and PSP, but focal slow waves appear to be characteristic only of CBD.[71]

Evoked potentials (EP)

Increased latency of the N200 and P300 components of the auditory evoked potential (AEP) and the N13 and N20 components of the somatosensory evoked potential (SEP)[72] have been observed in CBD but there are no data on the corresponding visual evoked potential (VEP). However, there have been a number of studies of event-related potentials in CBD, which elicit the 'P300' evoked response, believed to reflect orientation, attention, stimulus evaluation, and memory. These evoked responses may be associated with neural activity in the temporal lobe, prefrontal lobe, limbic system, and thalamus.[73] Hence, in a study of the P300 event-related evoked response in patients with CBD using a visual stimulus[73], the latency of the P300 was increased and mean reaction times were greater in CBD and in PSP than PD, the degree of the response being correlated with the extent of motor disability.[73] 'Giant' cortical evoked potentials of high amplitude, recorded in a diverse range of conditions of myoclonic or cortical origin, have also been reported in CBD.[74]

Complex visual functions

In a case of typical PCA but presenting as 'atypical CBD', the patient exhibited a decline in spatial orientation and visual function which included fixation, optic ataxia, agraphia, acalculia, ideomotor apraxia, but with preserved colour matching.[75] CBD patients may also exhibit difficulties in locating objects within a visual space.[53]

Hence, visuo-spatial dysfunction in CBD appears to be greater when it involves spatial rather than object-based tasks.[76] These impairments could be related to pathological changes affecting the frontal lobe[77] and visual association areas[78], the latter suggesting that CBD should also be considered as a possible diagnosis in the presence of PCA.

Sleep disorders

Sleep disorders, which include excessive daytime sleeping, have been recorded in parkinsonian syndromes[79] and are often caused by pathology affecting the regulation of the sleep/awake transitional period and respiratory function. Sleep behavioural disorder episodes often decrease in frequency but sleep becomes increasingly abnormal as disease develops.[80] 'Idiopathic rapid eye movement' (iREM) sleep behaviour disorder has been observed in some parkinsonian syndromes, characterized by abnormal behaviour during sleep accompanied by iREM, probably resulting from neuronal loss in locus caeruleus and substantia nigra.[81] So common is iREM in association with parkinsonism, that it is often regarded as a strong indicator of the presence of a parkinsonian syndrome. However, iREM appears rare in CBD, recent estimates suggesting an incidence of only 5%, and its absence could be a useful additional diagnostic feature.[54]

Visual hallucinations

Visual hallucinations have been reported in several parkinsonian disorders especially in individuals with significantly impaired visual acuity, severe cognitive impairment[82], and Lewy body pathology. Hence, hallucinations occur most commonly in DLB and PD, but are less common in PSP and CBD.[54,83,84]

Differential diagnosis of CBD

A number of general features of the disease are suggestive of a diagnosis of CBD. First, degeneration in CBD affects both sensory and motor systems giving rise to a mixed 'perceptual-motor' syndrome, particularly characteristic of CBD.[85] Second,

brain atrophy in CBD is often lateralized.[86] Hence, in CBD, left side atrophy is usually greater than right side resulting in lateralized clinical signs, although bilateral atrophy can affect the superior parietal cortex (SPC) and striatum.[86] There are also differences in the pattern of brain atrophy in CBD and PSP, greater midbrain atrophy affecting midbrain, pons, thalamus, and striatum in PSP while, atrophy, of dorsal frontal and parietal cortex is greater in CBD.[86]

If visual signs and symptoms are present, they may provide additional support for a diagnosis of CBD. First, different combinations of oculomotor abnormalities are present in parkinsonian syndromes especially involving saccadic eye movement (Table 3). Hence, CBD is characterized by normal saccadic velocity but with abnormalities in saccadic gain which may distinguish CBD from PSP.[68] Second, vertical saccade paralysis in PSP is also likely to distinguish this disorder from CBD.[64] Nevertheless, clinicians should also be alert to intermediate and 'atypical' cases of CBD, in which vertical saccades may be present accompanied by an early slowing of horizontal saccades and the absence of square-wave jerks.[62] Third, although changes in saccadic latency are common to the majority of parkinsonian disorders, increased saccadic latency ipsilateral to the side exhibiting apraxia is more likely to indicate CBD.[62] However, saccadic eye movement dysfunction may be more similar in CBD, PD, and DLB, making these disorders more difficult to distinguish using these signs. Additional visual features that may aid a diagnosis of CBD are first, the presence of significant visuo-spatial dysfunction involving spatial rather than object-based tasks.[76] Second, sleep disorders and visual hallucinations, unrelated to medication, are rare in CBD compared with PD and DLB, and their presence can often exclude CBD as a possible diagnosis.

Management of the disease

CBD can affect many aspects of life and a multidisciplinary approach to management and care is often necessary. Management of CBD involves physiotherapy to maintain mobility and prevent contractures, gait-training to improve mobility and decrease the risk of falls, and the use of social workers and occupational therapists to oversee the provision of equipment and home adaptation. An important problem in the clinical

management of the disease is that many subjects with CBD exhibit problems in communication resulting in their inability to 'narrate a coherent story'.[87] This defect is likely to result from impaired information integration, related to the degree of frontal and parietal lobe atrophy, and clinicians should be aware of this problem in communicating with patients.

Visual deficits in parkinsonian-type syndromes are often important in influencing overall motor function. Visually, CBD can be regarded as an oculomotor apraxia accompanied by impairment of visuo-spatial processing and can be markedly debilitating.[53] Hence, identifying and correcting the visual problems as far as possible can significantly reduce the chances that a patient will suffer a serious fall and improve quality of life. Optometrists can work in collaboration with the patient and health care providers to identify and manage the specific visual deficits of the patient. First, although significant decline in visual acuity has not been specifically demonstrated in CBD, it is typical of the parkinsonian syndromes in general[8-11] and should be investigated in any suspected case of CBD. Second, visual fields should be tested as the pathology is often lateralized which could result in a hemianopia.[55,56] Third, although photophobia is less likely[54] the external eye should be monitored as blepharospasm and possibly dry eye may be present, these features being an essentially treatable visual feature of parkinsonian syndromes.[59-61] Artificial tears can be used to help dry eyes while blepharospasm has been treated successfully with botulinum toxin A injected at the junction of the preseptal and pretarsal parts of the levator palpebrae and orbicularis oculi muscles.[57] Fourth, patients with difficulties in opening their eyelids may have 'lid crutches' fitted to spectacle frames that can hold the lids open. Fifth, CBD patients have a particular difficulty with saccadic eye movements and deficits in gaze control may influence 'stepping behaviour' which may increase the risk of trips or falls.[88] Balance training in combination with eye movement and visual awareness exercises have been shown to improve gaze control in PSP[89] and may also help in CBD. Hence, patients can be referred to physiotherapists or occupational therapists. Sixth, CBD patients may have difficult in locating objects in visual space[53,76] and strategies to improve object recognition in the home may be beneficial. In addition, to maximize visual acuity, cataract surgery, and appropriate refractive correction can improve motor outcomes and associated

therapies.

Additional methods of managing CBD include cognitive stimulation which, through various activities and exercises, may improve memory, problem-solving, and language capability while physiotherapy can be used to strengthen muscles and improve posture.[90] Dysphagia can be a problem in CBD and exercise may be employed to stimulate the nerves used to trigger the swallowing reflex. Dietary changes may be helpful which incorporate foods and liquids that are easier to swallow. Feeding tubes may be necessary in more severe cases especially where there is a risk of malnutrition and dehydration. In addition, general support and care are necessary as dystonia and immobility can lead to sores.[52]

Conclusions

CBD is a complex parkinsonian syndrome in which patients exhibit a variety of signs and symptoms affecting both sensory and motor function. The visual problems of CBD have been relatively little studied compared with the other parkinsonian syndromes[8-11] as the condition is rare and difficult to clinically diagnose.[42] The existing data suggest that the most important visual signs are increased latency of saccadic eye movements ipsilateral to the side exhibiting apraxia[62], impaired smooth pursuit movements[14], and visuo-spatial dysfunction especially involving spatial rather than object-based tasks[76], but with relatively preserved primary vision. If ocular signs and symptoms are present, then they may aid differential diagnosis. The optometrist can play an important role in managing the disease both in ensuring that visual problems are corrected as far as possible and in referring patients to relevant health professionals.

Conflict of interest statement

The author reports no conflicts of interest.

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Table 1. Comparison of presenting features, motor signs and symptoms, and brain regions affected in corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Alzheimer's disease (AD), and Parkinson's disease (PD)

	Disorder			
Feature	CBD	PSP	AD	PD
Presentation	Sudden onset Asymmetric limb clumsiness No rigidity or tremor	Variable Dystonic rigidity Speech problems Falls	Insidious onset Short-term memory problems	Insidious onset Impaired mobility Autonomic problems
Motor symptoms	Parkinsonism Alien hand syndrome Apraxia	Gait and balance affected Downward gaze dysfunction	Mild	Akinesia Rigidity Tremor
Brain regions affected	Asymmetric Frontal, parietal temporal cortex Basal ganglia	Greater midbrain atrophy Dorsal frontal and parietal cortex less affected	General cortical	Basal ganglia Later cortical

Table 2. Summary of visual signs and symptoms in corticobasal degeneration (CBD)

Ocular function	Change in CBD
Primary vision	Generally affected in parkinsonism syndromes[8-11] but few data specific to CBD[53] Photophobia less frequent than in PSP[54]
Visual fields	Hemianopia may be present due to lateralized pathology[55,56]
Eyelids	Apraxia of eyelid opening.[57] Blink reflex may be affected.[58] Blepharospasm often present[61]
Saccadic eye movements.	Increase in saccadic latency ipsilateral to side with ataxia[562,63] Early slowing of horizontal saccades in atypical case[62] Vertical saccade paralysis rare[64] Increasing error rate in complex tasks[64]
Smooth pursuit movements	'Jerky' smooth pursuit movements and restricted range of movement[14,64]
Square-wave jerks	Reported in CBD[66,68]
Nystagmus	Abnormal optokinetic nystagmus in a proportion of patients[53,69]
VOR	Normal in CBD[70]
EEG	Slowing of background activity and appearance of focal slow waves[71]
Evoked potentials	Abnormal auditory and somatosensory evoked potential[72] Presence of 'giant' potentials[74]

Event-related potentials	Abnormal P300 using visual stimuli[72]
Complex visual dysfunction	Difficulty in locating objects within visual space[53,76-78]
Sleep disorder	Rare but iREM in approx. 5% of patients[54]
Visual hallucinations	Rare unrelated to medication[54,82-84]

Abbreviations: EEG = Electroencephalogram, iREM = Idiopathic rapid eye movement sleep disorder, PSP = Progressive supranuclear palsy, VEP = Visual evoked responses, VOR = Vestibulo-ocular reflex

Table 3. Comparison of saccadic eye movement parameters in corticobasal degeneration (CBD) with other parkinsonian syndromes (PD = Parkinson's disease, PSP = Progressive supranuclear palsy (PSP), DLB = Dementia with Lewy bodies, MSA = multiple system atrophy (MSA) (? = Limited data)

	Syndrome				
Saccadic Parameter	CBD	PSP	PD	DLB	MSA
Velocity	-	+	-	-	-
Latency	+	+	+	+	-
Gain	+	+	+	+	?
Vertical saccadic paralysis	-	+	-	-	-
Anti-saccade error rate	-	+	+	+	?
Complex saccadic tasks	+	?	+	+	?

Titles to Figures

Fig 1. Coronal section of the striatum of the brain from a pathologically confirmed case of corticobasal degeneration (CBD). The figure shows enlarged lateral ventricles (LV), atrophy of the head of the caudate nucleus (CN), but more normal internal capsule (IC), external capsule (EC), claustrum (Cl), and putamen (PuT)

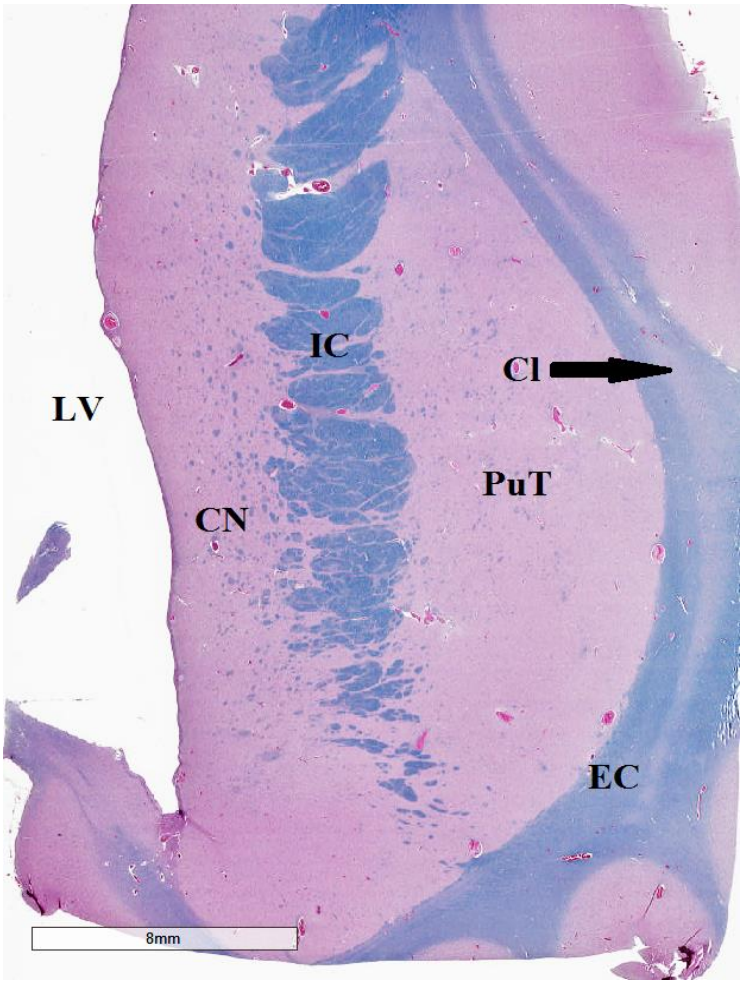

Fig 2. Tau-immunoreactive pathology in the superior frontal cortex of a case of corticobasal degeneration (CBD) showing features used in pathological diagnosis. Arrowheads = Neuronal cytoplasmic inclusions (NCI), Arrow = Astrocytic plaque, star = Dystrophic neurite (tau immunohistochemistry, antibody AT8; haematoxylin)

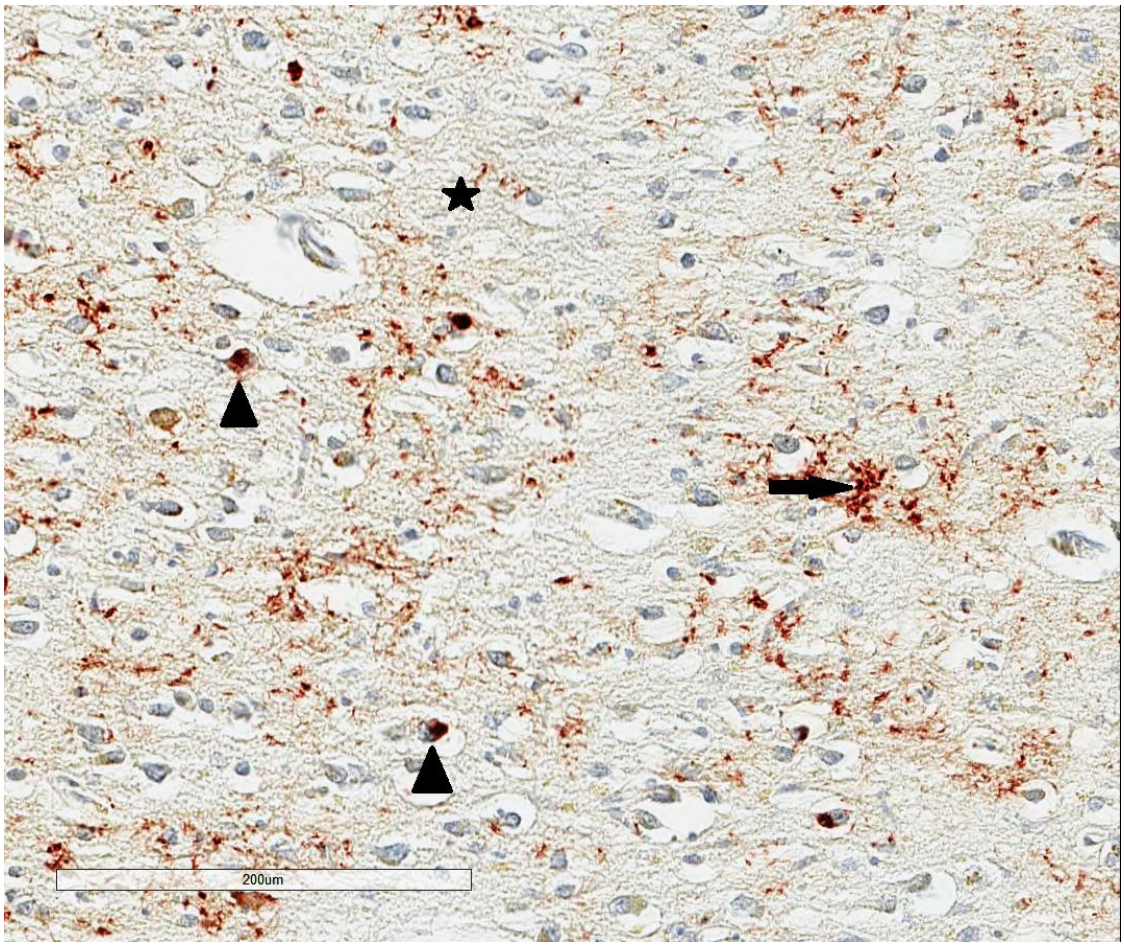

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Fig 3. The areas of the brain likely to be affected by the pathology of corticobasal degeneration (CBD) (shown in bold in large font) (A = Amygdala, CG = Cingulate gyrus, CN = Caudate nucleus, GP = Globus pallidus, HC = Hippocampus, MC = Motor cortex, P = Pons, PC = Parietal cortex, PHG = Parahippocampal gyrus, Pu = Putamen, SFC = Superior frontal cortex, SN = Substantia nigra, STG = Superior temporal gyrus, Th = thalamus, VT = Ventral tegmentum. Other areas less likely to be affected in CBD (in normal text and small font) (CB = Cerebellum, DG = Dentate gyrus, Hy = Hypothalamus, IC = Inferior colliculus, ION = Inferior olivary nucleus, LC = Locus careuleus, MB = Mamillary bodies, OB = Olfactory bulb, OC = Occipital cortex, PAG = Periaqueductal gray, PT = Pontine tegmentum, RH = Raphe nuclei, RF = Reticular formation, RN = Red nucleus, S = Septum, SC = spinal cord, STN = Subthalamic nucleus, SuC = Superior colliculus) superimposed on a two-dimensional model of the brain based on that of WJH Nauta and M Feirtag (1986) *Fundamental Neuroanatomy*. WH Freeman & Co. Hence the cerebral cortex is represented at the right of the diagram with the striatum and thalamus below. Midbrain and brain stem nuclei are at the left of the diagram