
In 1967, the neuropathologist E.P. Richardson and two colleagues from the Massachusetts General Hospital reported three patients with a progressive movement disorder, reminiscent of the condition described by Dr Richardson 3 years earlier that they named ‘corticodendatonigral degeneration’. Noting the unique pathological abnormalities, and expecting many similar examples to follow, in the event only a single further case was seen in Boston over the subsequent two decades. Writing in 1989, David Marsden and his colleagues have identified three additional patients with the disorder that they prefer to name ‘corticobasal degeneration’. This clinical experience has accumulated over a 4-year period during which 10 cases of Steele–Richardson–Olszewski syndrome were also observed.

Case 1, aged 67 years at onset, develops myoclonic jerks, tremor and spasm with fixed closure of his right hand, which soon becomes useless for all skilled movements. His voice is hoarse and he has blepharospasm. Everything increases with voluntary movement, touch or anxiety but improves somewhat with rest. His hand is atrophic and weak with a marked grasp reflex. He has constructional apraxia and difficulty with visuospatial organization. Physiological investigation suggests that the myoclonus is of cortical origin. There has been no response to a dopa-decarboxylase inhibitor or to carbamazepine, clonazepam or valproate. Later, he develops more generalized cognitive impairment, eventually leading to severe dementia that correlates with a gradual increase in the extent and distribution of temporal and parietal atrophy apparent on computerized tomography at presentation. Prior to his death, less than 5 years from onset, the patient is apathetic with fixed flexion of the right arm, which continues to jerk. The remaining limbs lack coordination and he is generally clumsy; clinical signs and electrophysiology together provide evidence for a mild axonal neuropathy. At presentation, Case 2 has an akinetic-rigid syndrome with constructional apraxia and a supranuclear disorder of eye movements. Initially, her cognitive function is otherwise relatively preserved. She has speech-induced limb chorea, orofacial dyskinesia, a pseudobulbar palsy and cerebellar symptoms. Over time Case 2 also deteriorates, showing no response to dopaminergic therapy, and she dies within 6 years from onset. Case 3, aged 66 years, notices difficulty in using her left hand, which levitates, wanders and floats uncontrollably. There is no response to medication and, later, she develops a generalized akinetic rigid syndrome that progressively interferes with skilled movements, and also has an eye movement disorder with some features of the Steele–Richardson–Olszewski syndrome. She often falls and has superimposed choreiform movements of the limbs. Death occurs within 5 years from presentation.

Neuropathological examination is performed in all three cases using formalin-fixed tissue. The abnormalities are regional and have specific histological features including characteristic neuronal inclusions. With some variations in distribution and extent, all three cases have extensive neuronal loss in the parietal cortex with disorganization of the usual cellular architecture. Demarcation between grey and white matter is blurred as a result of the extensive neuronal loss and demyelination of surviving axons. There are abnormalities in the basal ganglia and brain stem but the occipital cortex and hippocampus, medulla, cerebellar cortex and dentate nuclei are relatively spared. The putamen, caudate, globus pallidus, red nucleus, lateral thalamic nucleus, subthalamic nucleus, substantia nigra, periaqueductal region, superior colliculi, raphe nuclei, locus coeruleus and, to a lesser extent, the nucleus basalis of Meynert show similar histological changes to those present in the parietal, frontal and temporal cortices.

The neurons are swollen and occasionally vacuolated with eosinophilic and argyrophilic staining. They bear some resemblance to ballooned Pick cells (Fig. 1A). The deep cortical layers especially show astrocyte and microglial reactivity. There is no amyloid deposition, neurofibrillary tangles, senile plaques or Pick bodies in the affected regions. Neurons—especially in the substantia nigra, locus coeruleus and raphe nuclei—contain faintly basophilic fibrillar bodies, or pale inclusions surrounded by melanin granules, which, together, the authors designate as ‘corticobasal inclusions’ (Fig. 1B–D). These are somewhat reminiscent of, although distinct from, the inclusions seen in Pick’s disease and Steele–Richardson–Olszewski syndrome: ‘the main distinguishing point is that the filamentous skeins of corticobasal inclusions [are] barely visible, unlike the more distinct fibrillar component of globose tangles’.

Extensive search reveals only a single Lewy body (Fig. 1E).

Therefore, corticobasal degeneration typically presents with a focal movement disorder—dystonia, fixed flexion and the ‘alien’
hand—that evolves into an akinetic-rigid syndrome. The motor disorder is associated with constructional apraxia and a supranuclear abnormality of eye movement. Other movement disorders and more generalized upper motor neuron symptoms and signs in the limbs may occur. These features reflect involvement of the parietal and frontal lobes, the nigrostriatal pathway and the supranuclear corticobulbar pathways for gaze. The distinction on clinical grounds from Pick’s and Alzheimer’s diseases eventually becomes clear, but the condition may initially be confused with the Steele–Richardson–Olszewski syndrome. The neuropathology does not match the regional distribution characterizing that condition; nor does it show the regional pattern and cellular signatures of Pick’s disease. The newly described cases from London apparently have the same disorder as the three (or probably now four) reported previously from the Massachusetts General Hospital. Therefore, David Marsden’s team obtains tissue sections of the substantia nigra from these archival cases and makes direct comparison with their own material. Each of Dr Richardson’s cases has corticobasal inclusions; however, rather more Lewy bodies are present than in the London series. Probably, the literature does contain additional cases in which the same syndrome is present but not recognized, and therefore usually misdiagnosed.

Figure 1 (A) Case 1. Pick cell in the anterior parietal cortex. Swollen cell with homogenously eosinophilic, vacuolated cytoplasm. Bar = 100\( \mu \)m. (B) Case 1. Slightly basophilic faintly fibrillar inclusions containing melanin granules in the substantia nigra. Bar = 20\( \mu \)m. (C) Case 1. Pale body with a finely granular texture surrounded by melanin granules in the substantia nigra. Bar = 20\( \mu \)m. (D) Case 1. Neuronal change with eosinophilic degeneration in the substantia nigra. Bar = 20\( \mu \)m. (E) Case 1. Isolated Lewy body in the substantia nigra. Bar = 20\( \mu \)m.
as Steele–Richardson–Olszewski syndrome. Writing at a time when the concept of the frontotemporal dementias, with their increasingly well-recognized genetic and molecular characterizations were not appreciated, William Gibb and colleagues lay out the reasons why corticobasal degeneration is not the same as Pick’s disease. Neither the clinical features, the sharply demarcated lobar pathology usually sparing the parietal cortex and the basal ganglia, nor the characteristic cellular inclusions (Pick bodies) suggest overlap to the informed observer. But their reading of the extant literature is characteristically astute: ‘clinical and pathological features of [corticobasal degeneration] differ considerably from Pick’s disease, but extensive studies are required to clarify the correct classifications of variants of Pick’s disease, and disorders with progressive aphasia’.

By 1994, approximately 40 examples of the disorder first described from Boston have accumulated in the literature under the titles of ‘corticoginal degeneration with neuronal achromasia’, ‘cortical degeneration with swollen chromolytic neurons’ and ‘cortical–basal ganglionic degeneration’; but Professor Marsden’s group prefers to retain the nomenclature of ‘corticobasal degeneration’. Now they have 36 additional cases to report, most followed over several years and 6 with pathological confirmation of the clinical diagnosis. Seen after disease duration of around 3 years, typically the patients have presented with a clumsy hand that lacks skilled movement. Some have a stiff jerking limb alone or in combination with loss of movement; others first describe sensory alterations or, when the leg is initially affected, difficulty walking. Bulbar presentation has been seen in four cases. Over time, these symptoms deteriorate and spread, although one limb usually remains predominantly affected by rigidity, akinesia, touch-evoked myoclonus and both ideomotor and ideational apraxia with a fixed dystonic posture that clenches the fingers into the palm. Almost half of the patients have an alien limb that wanders and contaminates movement of the better arm: ‘[it has] a mind of its own… it just does not do what I want it to do… it does not belong to me’. Most lack balance, their gait showing a combination of short steps, shuffling and hesitation or impaired postural reflexes and falls. Almost half have dysarthria and features of a pseudobulbar palsy. Saccadic and pursuit eye movements are usually impaired, but with intact doll’s eye movements accounting for the confusion with Steele–Richardson–Olszewski syndrome. Pyramidal signs and loss of sensory discrimination are often present. Generalized intellectual loss is unusual, but evidence for parietal or frontal lobe dysfunction is present in several patients; these individuals usually have evidence from computerized tomography for focal brain atrophy. Towards the end of the illness, rigidity to the extent of uselessness in one or both arms with fixed dystonic posturing, myoclonic jerking and apraxia (if the rigidity allows this to be demonstrated) are almost invariable. Speech may be unintelligible, eye movements severely limited and sensation impaired, but intellectual deterioration is still rare at this late stage.

Taken together, these 36 cases reproduce the findings from previous descriptions and identify corticobasal degeneration as a stereotyped movement disorder of one limb that spreads with time, typically evolving into an asymmetric akinetic rigid syndrome with a useless jerking dystonic arm that wanders, an apraxic leg that interferes with walking, a supranuclear disorder of eye movements and sensory symptoms, but with the intellect generally preserved. The experienced clinician will easily discard the diagnosis of Parkinson’s disease. There are sufficient features to make the distinction from Steele–Richardson–Olszewski syndrome, although the hypometria and slowness followed by paresis of vertical saccades (especially for downgaze with square wave jerks and apraxia of eyelid opening typical of that condition) may also occur in corticobasal degeneration. The focal limb symptoms with alien limb suggest involvement of the medial frontal lobe; and the cortical myoclonus is due to the involvement of the sensory-motor cortex. Although focal onset of Alzheimer’s disease has been reported, this is unusual and, unlike corticobasal degeneration, any associated Parkinsonian symptoms and signs are usually symmetrical in that condition. Creutzfeld–Jacob disease progresses more rapidly, manifests generalized myoclonus and shows distinct electroencephalographic abnormalities. Frontal (frontotemporal) dementia is distinguished by personality change with dementia and a high familial recurrence rate; and the recently described syndromes of primary progressive aphasia do not have significant motor involvement.

The relationship to Pick’s disease requires more careful consideration. Personality changes and dementia with infrequent extrapyramidal symptoms and signs are reliable distinguishing features. But several of the histological features—swollen achromatic neurons and inclusions—are shared with corticobasal degeneration. Although others have described a predominantly motor variant of Pick’s disease associated with pathological changes that extend back from the frontal convexity to the prefrontal gyrus and also involve the basal ganglia, David Marsden and his colleagues think it more likely that these cases are wrongly classified and are examples of corticobasal degeneration. Indeed one of their 36 cases, presenting with a phenotype that suggests Pick’s disease, has the histological hallmarks of corticobasal degeneration. But this and other cases in the literature lead them to concede that ‘corticobasal degeneration and Pick’s disease [may] represent different expressions of a comparable or even identical pathological process; the pathological changes might depend upon the areas of the brain bearing the brunt of the disease. Whether [corticobasal degeneration and Pick’s disease] have the same or different causes remains to be discovered’. And the clinical overlap with Steele–Richardson–Olszewski syndrome is also not easily dismissed. These uncertainties anticipate the uncertainty now raised again by Helen Ling and colleagues who ask ‘Does corticobasal degeneration really exist? A clinicopathological reevaluation’ (page 2045).

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