subspecies of dipeptide protein have repeatedly shown that dipeptide inclusion burden and protein levels are much lower or non-existent in the spinal cord. The subtle differences between molecular pathology of C9orf72-positive ALS and FTD cases may hold an important clue to the pathophysiological mechanism of the hexanucleotide expansion itself.

Jakub Scaber and Kevin Talbot
Nuffield Department of Clinical Neurosciences, Oxford University, John Radcliffe Hospital, Oxford, OX3 9DU, UK

Correspondence to: Kevin Talbot
E-mail: kevin.talbot@ndcn.ox.ac.uk
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Presymptomatic anterior frontal involvement in corticobasal degeneration

This scientific commentary refers to ‘Astrogliopathy predominates the earliest stage of corticobasal degeneration pathology’ by Ling et al. (doi:10.1093/brain/aww256).

One of the biggest challenges in the development of treatment for neurodegenerative disorders is being able to spot the earliest signs of disease, given that the underlying pathological changes may commence many years before clinical features develop. While models of pathological staging and spread have been established for common neurodegenerative disorders, including Alzheimer’s and Parkinson’s disease, the pattern of presymptomatic spread of rarer conditions, such as the neurodegenerative tauopathy corticobasal degeneration (CBD), is less well characterized. In this issue of Brain, Ling et al. (2016) demonstrate early CBD pathology in three asymptomatic cases. The authors propose, by comparison with late-stage disease, that astrogial pathology dominates at this early stage, with an anterior–posterior gradient of pathological change in the frontal lobe during disease progression.

The Braak staging system used in Alzheimer’s disease (Braak et al., 2006) depicts a spread of tau pathology from medial temporal lobe structures to neocortical regions with disease progression. Similarly, current concepts of Parkinson’s disease indicate initial Lewy body pathology in the dorsal motor nucleus of the vagus and olfactory bulb, spreading to the midbrain and thereafter to neocortical structures (Braak et al., 2003). Several factors have been crucial to the development of these staging systems. First, both conditions are relatively common, and the existence of monogenic inherited forms has allowed more accurate study of disease mechanisms and progression. Second, the identification of ‘presymptomatic’ features such as mild cognitive impairment, hyposmia and REM sleep behaviour disorder has enabled better understanding of disease evolution. Third, techniques such as amyloid-β PET imaging and the use of CSF biomarkers have permitted identification of early or presymptomatic disease. Indeed, in the case of Alzheimer’s disease, the study of autosomal dominant forms using amyloid-β PET ligands (Bateman et al., 2012) indicates that the deposition of amyloid-β protein may commence up to 20 years
Several factors related to CBD have limited the applicability of such strategies, making the pathological study of early disease all the more critical. The relative rarity and lack of familial forms of CBD have made large cohort studies harder. No reliable early clinical features have been identified that predict the development of CBD, and CSF biomarker studies have not revealed a definitive pattern suitable for diagnostic use. PET imaging of tau pathology is at a relatively early stage and its role in CBD diagnosis is as yet unclear. Further complicating matters is the considerable clinico-pathological heterogeneity, whereby CBD can present with diverse clinical phenotypes, including progressive aphasia, atypical parkinsonism or phenotypes, including progressive CBD can present with diverse clinical features of asymmetrical apraxia, parietal neglect, sensory loss. However, many cases of this syndrome have different underlying pathology (Kouri et al., 2011). Diagnostic criteria for corticobasal syndrome (CBS), formerly thought to be synonymous with pathological changes of CBD, comprises typical features of asymmetrical apraxia, parkinsonism, myoclonus and cortical sensory loss. However, many cases of this syndrome have different underlying pathology (Kouri et al., 2011). Diagnostic criteria for corticobasal syndrome have recently been updated to reflect this heterogeneity (Armstrong et al., 2013), a factor which has also hampered early diagnosis of this condition.

In the present paper by Ling et al., three preclinical cases of CBD are described, two of which are previously published. This was part of a large study of 130 CBD cases from 12 brain banks in the UK, USA and Europe. The three cases were compared with six age-matched cases representing end-stage pathology. The total brain tau load was calculated as the sum of individual regional tau loads, determined as percentage area of involvement for each of 20 brain regions of interest immunostained for tau using AT8 antibody. These regions were chosen on the basis of their typical involvement in established CBD. All three cases were clinically asymptomatic, but even at this stage had widespread tau pathology in several regions of the brain typically affected in CBD. In all cases this was 4-repeat (4R) tau pathology, the type of tauopathy seen in CBD. Importantly, astrocytic plaques were the most prominent type of lesion in anterior frontal cortex and in corpus striatum. Total tau load was nine times greater at end stage than in the preclinical cases, but the anterior to posterior tau load ratio in frontal cortex was 12 times greater in the preclinical cases than in the end-stage cases. Interestingly, loss of nerve cells from substantia nigra was very mild or absent in these preclinical cases compared to end-stage cases where such cells can often be devastated and parkinsonian features are common (Armstrong et al., 2013).

The finding that astrocytic plaques predominate in early stages of disease is particularly intriguing and leads Ling and colleagues to suggest that CBD may represent an astrogliopathy with ‘secondary’ neuronal tauopathy. Physiological and pathological relationships between astrocytes and neurons remain poorly understood, but attention has recently been focused on the possibility that neurodegenerative diseases characterized by tau accumulation might be underpinned by astroglial pathology through the concept of ageing-related tau astrogliopathy (ARTAG) (Kovacs et al., 2016). This refers to a morphological spectrum of astroglial pathology detected by tau immunohistochemistry, especially with phosphorylation-dependent and 4R tau isoform-specific antibodies. ARTAG occurs mainly, but not exclusively, in elderly individuals and describes the presence of clusters of ‘thorny’ tau-immunoreactive astrocytes at glia limitans or white matter, or as more solitary cells within grey matter with fine, fibrillary processes. Although the clinical significance of ARTAG remains uncertain, it is not unreasonable to consider this form of pathology to have mechanistic implications. In this context, late onset forms of tauopathy, such as CBD, where an early astrogliopathy predominates, might well have their roots within this spectrum of disorder.

Few other cases of preclinical CBD have been published, increasing the

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**Figure 1**  Schematic depiction of proposed pathological spread in corticobasal degeneration. Astroglial tau pathology predominates in anterior frontal lobes and basal ganglia in early disease as described by Ling et al. (2016). Pathology involves more posterior frontal structures and substantia nigra in the intermediate stage depicted by Nishida et al. (2015). At late stage there is more posterior cortical involvement; neuronal loss is widespread and is the predominant pathology at this stage.
importance of these findings. Nishida et al. (2015) recently reported two cases of preclinical/early CBD, both of whom had anterior frontal tau pathology but a higher burden of neuronal and glial pathology in the posterior frontal lobe and substantia nigra compared to the current paper. Ling and colleagues propose that the cases reported in that paper represent an intermediate or early stage of CBD given the higher posterior frontal tau load, which adds further information relevant to the proposed pattern of pathological spread.

These observations led Ling et al. to postulate that striatal afferent connections to dorsolateral prefrontal cortex and basal ganglia circuitry might be the earliest neural network connections to be damaged and to fail in CBD. Moreover, because the most prominent tau lesions in these areas were astrocytic plaques, rather than neuronal tau (as neurofibrillary tangles, pretangles and neuropil threads), it is possible that CBD commences as pathology of astrocytes, though in later stages of disease this aspect of the pathological process subsides and neuronal changes become predominant. In summary, the study shows, as with other neurodegenerative diseases, that a threshold of pathological burden in appropriate brain regions has to be crossed in CBS before there is onset of clinical symptoms, and that the ultimate syndromic expression of disease is set very early in the course of the pathological process. Given that posterior frontal lobe involvement is seen in intermediate or more advanced stages, the authors propose that involvement of the precentral gyrus determines the threshold beyond which symptoms occur. Given the heterogeneity of the clinical syndromes with underlying CBD pathology (Kouri et al., 2011), one cannot reliably infer which clinical features would have been observed in these cases, although the authors speculate that two cases with particularly frontal and striatal involvement would be expected to have the classical CBS phenotype, whereas the other would be more likely to have features of frontotemporal dementia. Apart from providing pathogenetic insight, the finding of early anterior frontal cortical, and subcortical, tau pathology in preclinical disease may become helpful in predicting underlying CBD when using in vivo tau imaging. Conceptually, given that the sites of early tau pathology in Alzheimer’s disease lie in medial temporal lobe structures, with frontal lobe regions generally only affected in middle stage disease (Braak stages II–IV) when temporal lobe tau is florid and cognitive change apparent (Braak et al., 2006), a strong tau signal within frontal lobe regions and basal ganglia could help distinguish CBS preclinically from other tauopathies, particularly Alzheimer’s disease. The development of PET tracers to image tau pathology is at a relatively early stage currently, but preliminary reports suggest they may be useful in tracking changes in Alzheimer’s disease and may also demonstrate tau pathology in CBS (Maruyama et al., 2013). Whereas the novel tau PET ligand 18F-AV-1451 identifies mixed 3R and 4R tau pathology in carriers of the microtubule-associated protein tau (MAPT) mutation (Smith et al., 2016), binding to pure 4R tau pathology may be less avid (Lowe et al., 2016). Better understanding of the role of these PET ligands in imaging different types of tau pathology, as well as longitudinal clinical follow-up of subjects with novel patterns of increased uptake, may help to improve our ability to detect early or preclinical CBD pathology. This would greatly aid in the development of urgently-needed disease-modifying therapy for this aggressive neurodegenerative disorder.

Christopher Kobylicki1,2 and David M. Mann1

1Division of Neuroscience and Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
2Department of Neurology, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, UK

Correspondence to:
Professor David M. Mann
E-mail: david.m.mann@manchester.ac.uk
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