What is the role of TDP-43 in C9orf72-related amyotrophic lateral sclerosis and frontotemporal dementia?

This scientific commentary refers to ‘Timing and significance of pathological features in C9orf72 expansion-associated frontotemporal dementia’, by Vatsavayai et al. (doi:10.1093/brain/aww250).

The C9orf72 hexanucleotide repeat expansion mutation is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), accounting for up to 12% of all patients in an average ALS clinic population. At post-mortem, patients with the C9orf72 hexanucleotide repeat expansion have the typical pathology seen in sporadic ALS and FTD, in which transactive response DNA-binding protein of 43 kDa (TDP-43; encoded by TARDBP) is translocated from its normal nuclear location to form cytoplasmic aggregates. However, they also show additional pathological features in the form of RNA foci, containing the transcribed hexanucleotide repeats, and aggregates, which stain with antibodies against dipeptide repeat proteins, the product of non-ATG translation. The order in which these distinct molecular abnormalities develop, and whether each of these pathological features is a necessary or sufficient condition for the development of clinical disease, are currently key questions in ALS/FTD research. In this issue of Brain, Vatsavayai et al. describe two strikingly different pathological cases of C9orf72-positive FTD with excellent ante-mortem characterization that provide novel and provocative contributions to this debate (Vatsavayai et al., 2016).

Transcription of the C9orf72 hexanucleotide repeat expansion can be detected as sense and antisense RNA foci in the nucleus and cytoplasm. Despite being located in the non-coding region of the C9orf72 gene, the C9orf72 mutation is the most common genetic cause of ALS, including those associated with C9orf72 mutations, demonstrate cytoplasmic aggregation of TDP-43 in affected neurons. Mutations in TDP-43 can cause ALS or FTD, demonstrating that this protein is mechanistically related to the development of neurodegeneration, and not just an ‘innocent bystander’.

Glossary

Non-ATG repeat associated translation: The canonical form of protein translation in eukaryotes requires an initiating ATG sequence (which codes for methionine) on the template mRNA. It is now known that in DNA repeat disorders, including Huntington’s disease and C9orf72-ALS/FTD, translation can be initiated in the absence of an ATG start codon. The products of these atypical translation initiation events may contribute to neurodegeneration.

Transactivating responsive DNA binding protein-43 (TDP-43): At autopsy ~97% of cases of ALS, including those associated with C9orf72 mutations, demonstrate cytoplasmic aggregation of TDP-43 in affected neurons. Mutations in TDP-43 can cause ALS or FTD, demonstrating that this protein is mechanistically related to the development of neurodegeneration, and not just an ‘innocent bystander’.
the repeat sequence is translated through a non-canonical process called ‘repeat associated non-ATG’ (RAN) translation, into five different species of dipeptide protein, which also form intracellular aggregates. In addition, patients with C9orf72-related ALS/FTD usually have typical TDP-43 cytoplasmic inclusions at post-mortem. Importantly, multiple classical neuropathological studies have concluded that it is the distribution of TDP-43 pathology that correlates best with the clinical phenotype in C9orf72 patients (Davidson et al., 2016; Mackenzie et al., 2016). Various authors have thus proposed that dipeptide pathology must logically predate the development of TDP-43 pathology (Davidson et al., 2016), and others that TDP-43 pathology is essential for development of ALS/FTD (Mackenzie and Neumann, 2016). However, neither clinicopathological studies nor observations in mammalian models have yet allowed definitive inferences about the causal relationship between these pathological features or the temporal sequence in which they occur.

Case 2 presented by Vatsavayai et al. gives a rare insight into the temporal evolution of neuropathological features in C9orf72-positive FTD, because for the first time tissue is available from a patient with the C9orf72 hexanucleotide repeat expansion who underwent a brain resection for a separate clinical problem while in the preclinical phase of FTD. Moreover, it is from the temporal lobe, an area that commonly shows TDP-43 pathology in FTD cases. The absence of pathological TDP-43 cytoplasmic aggregation 6 years prior to clinical symptom onset, but its presence at death following the development and diagnosis of FTD confirms that dipeptide pathology and RNA foci may precede the development of TDP-43 pathology by years.

Is it therefore possible to have the clinical syndrome of FTD, and therefore presumably neurodegeneration, without TDP-43 inclusions? In another patient (Case 1) Vatsavayai et al. describe a typical history of clinically fulminant behavioural variant FTD but with relatively little evidence of neurodegeneration at autopsy, confined predominantly to the median pulvinar thalamic nucleus and the subgenual anterior cingulate cortex. This pattern of atrophy without marked frontotemporal atrophy has previously been reported by the same group in an imaging study in a subset of C9orf72-positive FTD patients (Lee et al., 2014), with similar findings in presymptomatic subjects (Rohrer et al., 2015). Even more striking is that the post-mortem examination of Case 1 showed only minimal TDP-43 neurites and no inclusions and did not fulfil the formal pathological criteria for the classification of FTD-TDP. Although this raises fundamental questions about the role of TDP-43 in FTD, Case 1 is currently a rare exception in the face of large case series confirming frontotemporal atrophy and TDP-43 positive inclusions as the usual features of C9orf72-related FTD.

Questions about the role of TDP-43 pathology in FTD are not new. Minimal TDP-43 pathology has previously been reported in a family with the C9orf72 hexanucleotide repeat expansion, in which the mother presented with behavioural variant FTD and had widespread dipeptide pathology but little TDP-43 pathology at post-mortem. Interestingly, her son also carried the hexanucleotide repeat expansion mutation and, on the background of a history of apparently stable learning difficulties, developed a rapidly progressive neurodegenerative condition in his 20s. He also had dipeptide pathology but no TDP-43 pathology at post-mortem. Again, relative absence of atrophy was reported in both patients though no comment was made on the pulvinar nuclei (Proudfoot et al., 2014). Another group gave similar reports of three FTD patients with no or mild atrophy and a relative absence of TDP-43 (Baborie et al., 2015).

The question then remains how C9orf72 positive patients with relatively little atrophy develop FTD. On a macroscopic level the work of Vatsavayai et al. revives the idea of ‘thalamic dementia’ in which the possibility of neuronal dysfunction in the absence of marked degeneration has been contemplated (Deymeer et al., 1989). This is supported by their previous findings of reductions in global connectivity in C9orf72-positive FTD patients that correlated with medial pulvinar atrophy (Lee et al., 2014). Does this mean that there are multiple pathways toward FTD in C9orf72 hexanucleotide repeat expansion carriers? And do these changes arise during ageing or is the thalamic phenotype of neurodevelopmental origin?

The absence of TDP-43 positive cytoplasmic aggregates cannot be taken as evidence that TDP-43 molecular dysfunction is not present. In Case 2, TDP-43 nuclear depletion was seen both in the presymptomatic surgical tissue and also in occasional cells without aggregates at post-mortem. Whether this is an early pathological phenomenon or an artefact cannot be determined. Although Case 1 did not demonstrate TDP-43 nuclear depletion at post-mortem, the presence of a few wispy threads of TDP-43 still hints at TDP-43 dysfunction. It is possible that a combination of different molecular features (RNA foci, dipeptide repeat proteins and TDP-43 mislocalization) may contribute to C9orf72-related neurodegeneration, but in different proportions in individual patients and that the subjects in the current study are simply outliers. The longstanding debate in the field of neurodegeneration about whether inclusions are intrinsically toxic or merely a terminal marker of protein dysfunction has not been resolved. TDP-43 dysfunction rather than aggregation could provide a better unifying explanation for the cases with little frontotemporal atrophy and TDP-43 pathology.

This publication is now the fourth independent report of absent or minimal TDP-43 pathology in a patient with C9orf72-related FTD. It is noteworthy that no such cases have been reported in ALS. Moreover, studies of the geographical distribution of all
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.

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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