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Better LATE than never: A new term for a common TDP-43 proteinopathy in amnesic dementia syndrome

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Understanding the neurobiology underlying dementias is of paramount importance as finding ways to prevent or treat these diseases is one of the biggest medical challenges of our time. Dementia symptoms in people over 65 are most commonly associated with Alzheimer's disease (AD) pathologies - brain atrophy and the accumulation of amyloid-beta (A β) and tau aggregates. A report recently published in *Brain* draws attention to another pathological association with dementia in people over 80 that they named "Limbic-predominant age-related TDP-43 encephalopathy" (or LATE) (Nelson et al., 2019).

The accumulation of TDP-43 (transactive response DNA-binding protein 43 kDa) pathology in the brain during ageing and in association with dementia and other neurodegenerative diseases is not a new observation (Spires-Jones, Attems, & Thal, 2017; Wyss-Coray, 2016). However this new paper based on a working group of international scientists is important as it highlights that amnesic dementia in late life is often mis-diagnosed as AD, when the neuropathologic changes are instead those they describe for LATE (LATE-NC). The clinical presentation is similar to AD, while the pathological features are TDP-43 aggregates similar to those seen in amyotrophic lateral sclerosis (ALS) and the frontotemporal dementia (FTD) cases that have TDP-43 pathology, albeit with distinct spatial and temporal accumulations from ALS/FTD (Nelson et al., 2019).

TDP-43 proteinopathy was first identified in 2006 in both ALS and FTD (Cairns et al., 2007; Neumann et al., 2006). Later it was found in cases of AD and reported to modify the clinical phenotype (Josephs et al., 2008), and it is now recognised to be a prevalent mis-folded protein both in cognitively normal ageing and neurodegenerative diseases, and is associated with cognitive decline in the 'oldest-old' (Wyss-Coray, 2016). In this report, Nelson and colleagues summarize data from large community-based studies and observe LATE-NC in >20% of cases over the age of 80. Genetic risk factors of LATE overlap both with FTLD-TDP and AD, and LATE is thought to be 100 times more prevalent than FTD syndromes. Based on these data, authors suggest that the public health impact of LATE may be on the same order of magnitude as AD (Nelson et al., 2019).

The authors propose a neuropathological staging scheme for LATE with pathology in stage 1 in amygdala, stage 2 spreading to hippocampus, and stage 3 spreading to middle frontal gyrus (Nelson et al., 2019). Further, this report offers diagnostic approaches to differentiate LATE-NC from FTD and AD. Behavioural and aphasic syndromes are more typical of FTLD-TDP and amnesic syndrome more typical of LATE-NC. Compared to AD, LATE has later onset of symptoms, more restricted involvement of limbic structures and presence of hippocampal sclerosis (HS), which is often unilateral (Amador-Ortiz et al., 2007). Subjects with impaired word list delayed recall (hippocampal-dependent) and relatively preserved verbal-fluency (neocortical-dependent) will be expected to show predominantly LATE-NC post-mortem (Nelson et al., 2011). Also, when PET scans for tau and amyloid do not correlate with the clinical severity in a patient with episodic memory loss and prominent HS, these findings will be suggestive of LATE.

So what is the importance of this paper with regard to clinical practice? By highlighting a relatively common and previously under-reported pathology, and putting this pathology clearly within a clinical framework, the authors have reminded the dementia research community of the fundamental need to understand what they are trying to treat. By assuming all amnesic syndromes in older patients are AD, researchers are missing potentially confounding co-pathologies and may actually be missing the key pathologic driver of cognitive decline, and therefore missing the key molecular pathway for

intervention. Introducing a post-mortem confirmation of the key pathologies associated with cognitive decline for at least a proportion of clinical cohorts would go some way to providing an assessment of the cohort being studied, rather than assuming the key pathology based on clinical presentation. The neuropathology community has developed detailed grading systems to standardise assessment of a number of pathologies such as p-tau, A β , α -synuclein, and cerebrovascular pathology, and this publication standardises the approach to TDP-43 assessment.

This report stresses the fact that although AD remains by far the most common cause of dementia, the clinician should also think of LATE, especially when the onset of symptoms are in advanced age. It will be interesting to see how our understanding of this condition will evolve over time and how the dementia research community will modify their approach to clinical trials to take account of this important confounding degenerative pathology in later life.

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