striatum, and hypothalamus).[5,9] However, local [^{11}C]DASB binding was increased in carriers of the *LRRK2* mutation but decreased in carriers of the A53T *SNCA* mutation. Longitudinal studies in genetic populations and in at-risk phenotypes tracking the transition to manifest motor disease are needed to determine whether the observed neurotransmitter changes are pathogenic or compensatory responses, or a combination of the two. Detailed clinical assessment of motor and non-motor symptoms is crucial because depression and weight changes can increase serotonergic binding in subcortical areas in patients with Parkinson's disease.[7]

*Katharina A Schindlbeck, *David Eidelberg*
Center for Neurosciences, The Feinstein Institute for Medical Research, Manhasset, NY 11030, USA
deidelbe@northwell.edu

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New terminology for a common TDP-43 proteinopathy

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Understanding the neurobiology underlying dementias is crucial, as finding ways to prevent or treat these diseases is one of the biggest challenges of modern medicine. Symptoms of dementia in people older than 65 years are most commonly associated with Alzheimer's disease pathology (ie, brain atrophy and the accumulation of amyloid β and tau aggregates). In a new study, Peter Nelson and colleagues[1] report another pathology associated with dementia, predominantly in people over 80 years, which they have termed limbicpredominant age-related TDP-43 encephalopathy (LATE).

The accumulation of inclusions of transactive response DNA-binding protein 43 kDa (TDP-43) in the brain during ageing, in association with dementia or other neurodegenerative diseases, is not a new observation.[2,3] However, the study by Nelson and colleagues[1] highlights that amnestic dementia in late life might be often misdiagnosed as Alzheimer's disease although the patient can instead have neuropathological changes characteristic for LATE. LATE neuropathological change (LATE-NC) is defined by TDP-43 aggregates similar to those of amyotrophic lateral sclerosis and frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP), albeit with distinct spatial and temporal accumulations, and often including hippocampal sclerosis, but the disease's clinical presentation is similar to that of Alzheimer's disease.[1]

TDP-43 proteinopathy was first described in patients with amyotrophic lateral sclerosis and in those with frontotemporal dementia.[4,5] Subsequently, it was found in some patients with Alzheimer's disease and was reported to modify their clinical phenotype.[6] TDP-43 is now recognised to be a prevalent misfolded protein, both in cognitively normal ageing and in neurodegenerative diseases, and is associated with cognitive decline in the oldest old (>80 years of age).[3] In their report,[1] Nelson and colleagues summarise data from large community-based studies that included more than 1300 patients and find LATE-NC in more than 20% of cases older than 80 years. Genetic risk factors for LATE overlap with those for both FTLD-TDP and Alzheimer's disease, and LATE is estimated to be 100 times more prevalent than frontotemporal dementia syndromes, suggesting that the burden of LATE could be of a similar scale to that of Alzheimer's disease.[1]

Nelson and colleagues propose a neuropathological staging scheme for LATE, with TDP-43 pathology at stage 1 in the amygdala, spreading to the hippocampus at stage 2, and spreading to the middle frontal gyrus at stage 3. This staging scheme might differentiate LATE-NC from FTLD-TDP or Alzheimer's disease pathology. As the TDP-43 aggregates begin to spread from the limbic areas in LATE-NC, the clinical presentation of this disease is associated with an amnestic syndrome, whereas behavioural and aphasic syndromes are linked to FTLD-TDP because of neocortical involvement.[7] However, symptoms of Alzheimer's disease reflect both neocortical (ie, impaired verbal fluency) and hippocampal (ie, delayed word recall) involvement, rather than the severe hippocampal pathology leading to sclerosis, which is associated with LATE-NC.[8] Compared with patients with Alzheimer's disease, patients with LATE have a delayed onset of symptoms (typically over 80 years of age), predominant episodic memory impairment, and a more restricted involvement of limbic structures on imaging. Also, when PET scans for tau and amyloid β do not correlate with the clinical severity in a patient with episodic memory loss and prominent hippocampal sclerosis, these findings will be suggestive of LATE.

So what is the importance of these findings for clinical practice? By highlighting a relatively common and previously underreported pathology of TDP-43, and putting this pathology clearly within a clinical framework, the authors have reminded the dementia research community of the fundamental need to understand the diseases that they are trying to treat. By assuming that all amnestic syndromes in older patients are Alzheimer's disease, researchers and clinicians are missing potentially confounding co-pathologies and might actually be missing the key pathological driver of cognitive decline in these patients, thus identifying the wrong molecular pathway to target. Post-mortem confirmation of the key pathologies associated with cognitive decline for at least a proportion of clinical cohorts would provide an accurate assessment, rather than assuming the cohort's key pathology on the basis of clinical presentation. The neuropathology community has already developed detailed grading systems to standardise the assessment of pathologies, such as phosphorylated tau, amyloid β, α-synuclein, or cerebrovascular pathology, and the staging scheme of Nelson and colleagues can standardise the approach to TDP-43 assessment.

Their study stresses the fact that, although Alzheimer's disease is by far the most common cause of dementia, clinicians should also think of LATE, especially when the onset of symptoms occur in advanced age. It will be interesting to see how the dementia research community's understanding of this condition will evolve over time and how that will modify their approach to clinical trials.

*Hatice Kurucu, *Tara Spires-Jones, Colin Smith*
UK Dementia Research Institute, Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh W1T 7NF, UK (HK, TS-J) and Academic Department of Neuropathology, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK (CS)
tara.spires-jones@ed.ac.uk

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The trinity of tau, trauma, and time

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Chronic traumatic encephalopathy (CTE) is, according to neuropathological diagnostic criteria, a progressive, neurodegenerative tauopathy associated with a history of repetitive head trauma. However, clinical diagnostic criteria have not been established. In a novel study,[1] the PET tracer flortaucipir was used to measure tau burden while florbetapir was used to measure amyloid-β burden in the brains of 26 former National Football League