Serotonergic pathology and Braak's staging hypothesis in Parkinson's disease

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The gene encoding for α-synuclein (*SNCA*) was the first to be linked to familial Parkinson's disease.[1] At the same time, α-synuclein was identified as the main component of Lewy bodies, which are present in both familial and idiopathic Parkinson's disease.[2] The Ala53Thr (A53T) *SNCA* mutation is associated with a similar clinical phenotype to the sporadic disease, albeit with earlier age-of-onset and faster disease progression.[3,4]

In *The Lancet Neurology*, Heather Wilson and colleagues[5] report findings from a PET imaging study in A53T *SNCA* mutation carriers with (n=7) and without (n=7) clinically manifest Parkinson's disease, compared with patients with idiopathic Parkinson's disease (n=25) and healthy controls (n=25). In these four groups the authors used [^{11}C]DASB PET to measure serotonergic transporters in conjunction with [^{123}I]FP-CIT single proton emission CT (SPECT) to measure dopamine transporters. Even though premotor A53T *SNCA* carriers had normal dopaminergic function and normal wrist actigraphy, these participants had significant decreases in serotonergic binding localised to the raphe nuclei, caudate, putamen, thalamus, hypothalamus, and amygdala compared with healthy controls. In the A53T *SNCA* carriers with clinically manifest Parkinson's disease, serotonergic transporter loss extended to the hippocampus, cingulate, insula, and neocortical areas, and loss of striatal dopamine transporters was also evident. These findings show the presence of serotonergic pathology in premotor A53T *SNCA* carriers even before the development of striatal dopaminergic loss and the appearance of motor manifestations. These results conform with Braak's staging hypothesis,[6] which suggests a caudorostral spread of α-synuclein deposition beginning in the medulla and proceeding to the pons and midbrain levels before affecting the forebrain and neocortical regions. Importantly, premotor carriers of the A53T *SNCA* mutation had serotonergic pathology in brain areas that are hypothesised to underlie pre-symptomatic disease (Braak stages 1–3). By contrast, clinically manifest carriers exhibited similar pathology but involving mesocortial and neocortical regions affected at more advanced disease stages (Braak stages 4–6).

The authors also compared the transporter changes in A53T *SNCA* carriers with those in patients with idiopathic Parkinson's disease. The severity of the serotonin transporter loss in premotor carriers was noted to be at levels typically seen in idiopathic patients. Moreover, carriers with manifest disease showed greater loss of both serotonin and dopamine transporters in the caudate compared with age-matched idiopathic patients. These findings point to similar pathophysiological mechanisms but with a more aggressive disease course in A53T *SNCA* carriers compared with patients with idiopathic Parkinson's disease. Nonetheless, this conclusion must be confirmed in longitudinal studies.

Localised decreases in serotonergic transporter binding are a common finding in patients with Parkinson's disease, and have been associated with a variety of symptoms, including tremor and levodopa-mediated dyskinesias, and non-motor symptoms such as depression, fatigue, apathy, and weight changes.[7] In the present study, brainstem serotonergic binding loss correlated with motor and non-motor symptoms in idiopathic Parkinson's disease patients and in A53T *SNCA* carriers with and without manifest disease. The authors propose that [^{11}C]DASB PET measures might serve as quantitative imaging biomarkers of Parkinson's disease progression in individual patients. However, such an application would require thorough validation to show the stability and sensitivity of radioligand binding measures in longitudinal cohorts of patients with idiopathic Parkinson's disease and A53T *SNCA* carriers.

Overall, these findings add to the growing body of evidence from other studies using neurotransmitter imaging in pre-manifest mutation carriers and in premotor conditions of Parkinson's disease. These studies provide in-vivo evidence that the disease begins in the noradrenergic, serotonergic, and autonomic nervous system and follows a caudorostral gradient of neurotransmitter deficits that parallels the Braak's staging hypothesis.[8–10] In this regard, a cross-sectional PET study[9] showed increased serotonin binding in non-manifest carriers of the *LRRK2* mutation, whereas decreases were present in *LRRK2* carriers with Parkinson's disease and in idiopathic patients, compared with healthy controls.[9] Interestingly, non-manifest *LRRK2* and A53T *SNCA* carriers seem to have serotonergic abnormalities in the same brain regions (brainstem,

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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1 Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 1997; **276:** 2045–47.
2 Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. *Nature* 1997; **388:** 839–40.
3 Kim CY, Alcalay RN. Genetic forms of Parkinson's disease. *Semin Neurol* 2017; **37:** 135–46.
4 Papadimitriou D, Antonelou R, Miligkos M, et al. Motor and nonmotor features of carriers of the p.A53T alpha-synuclein mutation: a longitudinal study. *Mov Disord* 2016; **31:** 1226–30.
5 Wilson H, Dervenoulas G, Pagano G, et al. Serotonergic pathology and disease burden in the premotor and motor phase of A53T α-synuclein parkinsonism: a cross-sectional study. *Lancet Neurol* 2019; **18:** 748–59.
6 Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; **24:** 197–211.
7 Pagano G, Niccolini F, Fusar-Poli P, Politis M. Serotonin transporter in Parkinson's disease: a meta-analysis of positron emission tomography studies. *Ann Neurol* 2017; **81:** 171–80.
8 Knudsen K, Fedorova TD, Hansen AK, et al. In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. *Lancet Neurol* 2018; **17:** 618–28.
9 Wile DJ, Agarwal PA, Schulzer M, et al. Serotonin and dopamine transporter PET changes in the premotor phase of *LRRK2* parkinsonism: cross-sectional studies. *Lancet Neurol* 2017; **16:** 351–59.
10 Liu SY, Wile DJ, Fu JF, et al. The effect of *LRRK2* mutations on the cholinergic system in manifest and premanifest stages of Parkinson's disease: a cross-sectional PET study. *Lancet Neurol* 2018; **17:** 309–16.

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]