

## IN BRIEF

## PARKINSON DISEASE

**Increased  $\alpha$ -synuclein levels in patients with sleep apnoea might be involved in PD pathogenesis**

Plasma levels of  $\alpha$ -synuclein — aggregates of which are the pathological hallmark of Parkinson disease (PD) — are increased in patients with obstructive sleep apnoea syndrome (OSAS) and correlate with the degree of hypoxia, according to a new study. Sun et al. measured total and phosphorylated  $\alpha$ -synuclein levels in 42 patients with OSAS and 46 age-matched and gender-matched controls who had simple snoring. Total and phosphorylated  $\alpha$ -synuclein levels were significantly higher in patients with OSAS than in controls and correlated positively with the apnoea–hypopnoea index and the oxygen desaturation index. Total and phosphorylated  $\alpha$ -synuclein levels were negatively correlated with mean and lowest oxyhaemoglobin saturations. Previous studies suggest that OSAS is a risk factor for onset of PD; the authors say their findings indicate that chronic hypoxia increases  $\alpha$ -synuclein levels and might be involved in the pathogenesis of PD.

**ORIGINAL ARTICLE** Sun, H.-L. et al. Plasma  $\alpha$ -synuclein levels are increased in patients with obstructive sleep apnea syndrome. *Ann. Clin. Transl. Neurol.* <https://doi.org/10.1002/acn3.756> (2019)

## MOTOR NEURON DISEASE

**Arginine dimethylation is increased in patients with ALS and can predict disease progression**

Patients with amyotrophic lateral sclerosis (ALS) have increased arginine dimethylation, and an asymmetrical dimethylarginine (ADMA) to L-arginine ratio could be a predictor of prognosis, say researchers. Ikenada and colleagues report that the immunoreactivity of protein arginine methyltransferase 1 (PRMT1) and its products in post-mortem spinal cord was increased in cord from four patients with ALS compared with cord from four patients without ALS. They also found that the concentration of ADMA in cerebrospinal fluid was significantly higher in 52 patients with ALS than in 21 controls. The team also showed that the ADMA to L-arginine ratio correlated with the rate of decline in the ALS Functional Rating Scale and that the ratio was an independent predictor of overall survival. A high ADMA to L-arginine ratio was a predictor of poor prognosis.

**ORIGINAL ARTICLE** Ikenada, K. et al. Increase of arginine dimethylation correlates with the progression and prognosis of ALS. *Neurology* <https://doi.org/10.1212/WNL.0000000000007311> (2019)

## MULTIPLE SCLEROSIS

**Dimethyl fumarate is more effective than teriflunomide in preventing relapse in RRMS**

A new study reports that dimethyl fumarate might be more effective than teriflunomide in preventing relapses in patients with relapsing–remitting multiple sclerosis (RRMS). The study by Buron et al. included 2,236 patients with RRMS — 1,469 on teriflunomide and 767 on dimethyl fumarate. Annualized relapse rates were lower among patients on dimethyl fumarate than among those on teriflunomide (0.09 versus 0.16). Relapse-free survival rate after 48 months of follow-up was significantly greater in patients on dimethyl fumarate, and the incidence of discontinuation due to disease breakthrough was lower in the dimethyl fumarate group (10.2% versus 22.1%). The results were similar after adjustment for the potential confounding effects of baseline MRI T2 lesion number.

**ORIGINAL ARTICLE** Buron, M.D. et al. Comparative effectiveness of teriflunomide and dimethyl fumarate: a nationwide cohort study. *Neurology* <https://doi.org/10.1212/WNL.0000000000007314> (2019)

## STROKE

**A role for double-negative T cells in post-stroke neuroinflammation**

A new study has identified a key role for CD3<sup>+</sup>CD4<sup>−</sup>CD8<sup>−</sup> T cells, also known as double-negative T cells (DNTs), in neuroinflammation after ischaemic stroke. Yu Xu and colleagues at Nanjing University in China found evidence of DNT involvement in post-stroke neuroinflammation in patients and animal models, and they suggest that these cells could provide a target for novel stroke therapies.

“Previous studies assessing the mechanism by which T cells regulate immune and inflammatory responses in the brain during stroke have mainly focused on CD4<sup>+</sup> helper and CD8<sup>+</sup> cytotoxic T cells, which comprise ~95% of T cells,” the authors write in the new paper. “Despite DNTs accounting for a small percentage (1–5%) of T cells in the peripheral blood and lymphoid organs, they play important roles in many diseases.”

The researchers found that levels of DNTs were elevated in the blood of

patients following ischaemic stroke. Analysis of post-mortem brain slices from patients with stroke revealed accumulation of DNTs in the ischaemic penumbra — that is, the at-risk but not yet infarcted tissue surrounding the ischaemic core. The DNTs were found to colocalize with pro-inflammatory microglia in this region.

In a mouse model of stroke, Xu and colleagues observed that the infiltrating DNTs expressed increased levels of the anti-inflammatory protein PTPN2 and reduced levels of the pro-inflammatory cytokine TNF. In co-culture experiments in vitro, PTPN2 inhibition in DNTs increased the expression of TNF and promoted the activation of pro-inflammatory microglia.

“These data reveal that infiltrating DNTs are the critical driving force in promoting microglia-mediated neuroinflammation and ischaemic brain injury,” the authors conclude.

## CEREBROVASCULAR DISEASE

**Perivascular spaces are associated with cognition**

Perivascular spaces (PVS) are a marker of cognition in older adults without dementia, and might operate through a unique pathway of injury, according to a new study.

“Small vessel disease markers are largely thought to reflect ischaemic changes in the brain,” explains corresponding author Angela Jefferson. “However, there is a great need to better understand the degree of pathological overlap in these markers, and importantly, their clinical significance.”

The study included 327 older adults (mean age 73 years) without dementia. Participants underwent a detailed neuropsychological assessment to assess global cognition, language, visuospatial skills, information processing speed, executive function and episodic memory. Various markers

of small vessel disease, including white matter hyperintensities (WMH), PVS, cerebral microbleeds (CMBs) and lacunes, were assessed by MRI.

“We found that each marker of small vessel disease related to cognitive activities in some way,” says Jefferson. “As expected, the most frequent associations we saw were between WMH and cognition, including language, information processing speed, executive functioning and visuospatial skills. Unexpectedly, the next most frequent associations were between enlarged PVS and information processing speed and executive functioning.” CMBs and lacunes were associated with fewer cognitive measures than expected.

“We also wanted to know whether these imaging markers overlapped in their association with cognition, suggesting a common pathway of