IN BRIEF

MULTIPLE SCLEROSIS

Phase II trial of evobrutinib in multiple sclerosis

In patients with relapsing multiple sclerosis (MS), daily treatment with a 75 mg dose of the BTK inhibitor evobrutinib reduces the total number of gadolinium-enhancing lesions on T1-weighted MRI, according to a randomized phase II trial. Montalban and colleagues randomly assigned 267 patients with MS to placebo, evobrutinib (25 mg once daily, 75 mg once daily or 75 mg twice daily) or open-label dimethyl fumarate (as a reference). Patients who received 75 mg evobrutinib once daily had significantly fewer gadolinium-enhancing lesions during weeks 12–24 than those who received placebo. The other doses had no significant effects on lesion numbers, and none of the doses reduced annualized relapse rates. In addition, evobrutinib treatment was associated with increased liver aminotransferase levels. The authors say that larger studies are needed to weigh up the risks and benefits of this drug.

ORIGINAL ARTICLE Montalban, X. et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1901981 (2019)

NEURODEGENERATIVE DISEASE

Abnormal gyrification patterns present before symptoms in *C9orf72* expansion carriers

Repeat expansions in *C9orf72* are a frequent cause of amyotrophic lateral sclerosis and frontotemporal dementia. A new study reports that individuals with these repeat expansions show abnormalities in gyrification (cortical folding) before symptoms appear. Caverzasi et al. investigated patterns of cortical gyrification and thickness in 15 presymptomatic *C9orf72* expansion carriers and 67 age-matched and sex-matched controls. Presymptomatic *C9orf72* expansion carriers showed a lower local gyrification index in left frontal and right parieto-occipital regions compared with controls. Gyrification measurements did not correlate with cortical thickness measurements in presymptomatic carriers or healthy controls, suggesting that gyrification is a novel grey matter metric that is distinct from cortical thickness.

ORIGINAL ARTICLE Caverzasi, E. et al. Gyrification abnormalities in presymptomatic *c9orf72* expansion carriers. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2018-320265 (2019)

HUNTINGTON DISEASE

ADAM10 inhibition shows promise in HD

Inhibition of ADAM10 has therapeutic potential in Huntington disease (HD), say researchers. Vezzoli et al. found that striatal levels of the mature active form of ADAM10 were increased in patients with HD and mouse models of the condition. Using a mouse model and post-mortem caudate tissue from patients with HD, the researchers demonstrated that mature ADAM10 accumulated at the synapse, leading to increased proteolysis of N-cadherin, which resulted in compromised adhesion between the presynaptic and postsynaptic membrane. The researchers showed that allele-specific downregulation of mutant huntingtin protein could prevent the increases in mature ADAM10 levels and N-cadherin proteolysis. Further experiments showed that administration of an ADAM10 inhibitor improved the functional defects at the synapse in HD mouse models, and that heterozygous deletion of ADAM10 in the forebrain prevented synapse loss and synaptic ultrastructural defects in the striatum of HD mice, thereby reducing cognitive impairment.

ORIGINAL ARTICLE Vezzoli, E. et al. Inhibiting pathologically active ADAM10 rescues synaptic and cognitive decline in Huntington's disease. *J. Clin. Invest.* https://doi.org/10.1172/JCI120616 (2019)

PRION DISEASE

Neurogranin in CSF identifies Creutzfeldt–Jakob disease

A high neurogranin concentration in the cerebrospinal fluid (CSF) is a biomarker of Creutzfeldt–Jakob disease (CJD) and can differentiate between patients with CJD and those with Alzheimer disease (AD), according to a new study. Neurogranin levels had diagnostic and prognostic value, and were associated with the degree of neuronal damage in the brain.

Neurogranin is involved in neuronal plasticity and long-term potentiation, and elevated CSF levels of the protein have previously been identified as a marker of AD. "Although extensive work has been done in AD, data are lacking regarding neurogranin levels in other diseases that involve substantial synaptic and neuronal loss, such as CJD," explains Franc Llorens, who led the new study. "We aimed to investigate whether CSF neurogranin concentrations were altered in CJD compared with AD, and whether they were associated with neuronal degeneration in brain tissue."

The researchers measured CSF levels of neurogranin, total tau, neurofilament light and 14-3-3, all of which are associated with neurodegeneration, in 81 patients with CJD, 46 patients with AD, and 64 controls with non-degenerative neurological diseases. Neurogranin levels were increased in patients with AD and in patients with CJD relative to controls, but were highest among patients with CJD. The measure was poor at distinguishing patients with AD from controls, but accurately identified patients with CJD and distinguished them from patients with AD. Post-mortem analysis of brain tissue showed that the increases in CSF levels of neurogranin were accompanied by corresponding reductions of the protein in the cortex.

NEURODEVELOPMENTAL DISORDERS

Novel insights into autism from single-cell genomics

Through the use of single-cell genomics, a team led by Dmitry Velmeshev and Arnold Kriegstein at the University of California, San Francisco has uncovered gene expression changes in specific brain cell types and signalling pathways in individuals with autism spectrum disorder (ASD). The findings, which were published in *Science*, could aid the identification of new therapeutic targets for this condition.

"This study was made possible by a very recent technological advance that allows profiling of gene expression in single cells through the sequencing of nuclear RNA," explains Kriegstein. The researchers applied this single-nucleus RNA sequencing (snRNA-seq) technique to post-mortem prefrontal cortex (PFC) and anterior cingulate cortex tissue samples from 15 patients with ASD and 16 age-matched controls.

The analysis identified 513 differentially expressed genes (DEGs) between ASD and control samples. The gene expression changes were localized predominantly to upper-layer cortical neurons — in particular, layer 2/3 (L2/3) and L4 excitatory neurons — and microglia.

Detailed analysis of the neuronal DEGs in patients with ASD revealed downregulation of genes that are required for synaptic signalling and brain development. The microglial DEGs showed enrichment for genes that encode components of developmental and microglial activation pathways.

Velmeshev and colleagues also performed snRNA-seq on PFC samples from eight individuals with epilepsy. "Epilepsy is a comorbidity for many patients with ASD, and analysing these samples allowed us to remove changes due to seizures and antiseizure medication from the gene expression