In the news

THE UPS AND DOWNS OF ESOC 2018

Over 4,500 participants saw the first presentation of results from a raft of trials at the 4th European Stroke Organisation Conference (ESOC) in Gothenburg, Sweden, in May. The findings provided multiple insights into stroke management, both positive and negative.

Most notable among the negatives was the NAVIGATE-ESUS trial, which tested the safety and efficacy of the anticoagulant rivaroxaban against aspirin for secondary prevention in patients with embolic stroke of undetermined source (ESUS). The trial was terminated early because rivaroxiban was no more effective than aspirin at preventing recurrent stroke, and was associated with a significantly higher risk of major bleeding and intracranial haemorrhage.

More encouraging were retrospective analyses of thrombectomy and thrombolysis trials. The AURORA trial was a pooled analysis of five trials of the use of thrombectomy beyond the standard 6 h window. The analysis confirmed that thrombectomy is highly effective when administered up to 24 h after stroke in selected patients. Similarly, a meta-analysis of randomized controlled trials of alteplase presented at the conference demonstrated that the benefits of thrombolysis were unaffected by sex, hypertension, prior stroke, aspirin use and prognostic score.

A 5-year follow-up of the TIA registry was also presented, revealing that the risk of ischaemic events or stroke after a transient ischaemic attack (TIA) or minor ischaemic stroke continues to increase beyond the first year and for at least 5 years. This increase was observed despite optimal risk management, highlighting the need for further work to reduce the long-term risk in patients with TIA or minor ischaemic stroke. Results of the CROMIS-2 study showed that in patients with atrial fibrillation who received anticoagulants after a TIA, microbleeds detected with MRI were predictive of intracranial haemorrhage. However, the findings were not sufficient to identify patients who should not receive anticoagulants.

Finally among the trial highlights, the results of the TICH-2 trial were mixed. The study tested the use of tranexamic acid in patients with intracerebral haemorrhage with symptom onset less than 8 h previously. Compared with placebo, the treatment had no effect on disability after 90 days. However, tranexamic acid did reduce the number of deaths in the days after intracerebral haemorrhage; larger studies will be needed to determine whether this effect is significant.

Also at ESOC 2018, the European Stroke Organisation presented the Action Plan for Stroke in Europe 2018–2030, which was developed in cooperation with the Stroke Alliance for Europe. Effectively a third Helsingborg Declaration, the Action Plan sets out targets for improving stroke services across the continent and ensuring provision of resources that match the societal impact of the disease. The plan covers seven domains, across which a total of 31 targets have been set for 2030. Four overarching targets apply to all domains, and include a reduction in the number of strokes in Europe by 10%, and treatment of at least 90% of patients with stroke in dedicated stroke units.

Ian Fyfe

ALZHEIMER DISEASE

APOE4 transforms the transcriptome

A genetic switch from apolipoprotein E (*APOE*)*ε3* to *ε4* provokes features of Alzheimer disease (AD) in cells from healthy individuals, new research has shown. Researchers found that the substitution altered the expression of hundreds of genes in these cells.

The *APOE*ε4* allele is the strongest known genetic risk factor for sporadic AD. Its protein product, APOE4, promotes AD pathogenesis, but the mechanisms by which it achieves this effect in different cell types are unknown.

"We wanted to address the cell type-specific functions of APOE4 in astrocytes, neurons and microglia, particularly with respect to AD pathology," explains corresponding author Li-Huei Tsai. To achieve this aim, the team exploited the fact that APOE4 differs by only a single amino acid from APOE3 — a variant not associated with a risk of AD.

Tsai and colleagues created induced pluripotent stem cells (iPSCs) from individuals without AD and used the CRISPR–Cas9 gene-editing system to change the *APOE*ε3* allele into the *ε4* variant in these cells. The researchers then carried out transcriptional profiling on neurons, astrocytes and microglia-like cells generated from their *APOE*ε3* and *APOE*ε4* iPSCs.

"Surprisingly, a switch from APOE3 to APOE4 had a dramatic impact on the transcriptome of neurons and glial cells, significantly altering expression of hundreds of genes, particularly those involved in synaptic function in neurons, lipid metabolism in astrocytes and immune responses in microglia-like cells," explains Tsai. These transcriptome changes manifested as an increased number of synapses and increased amyloid-β $(Aβ)_{42}$ release in neurons, disrupted Aβ uptake

CNS INFECTIONS

Targeting TNF to alleviate Zika virus complications

Congenital Zika virus (ZIKV) infection can induce an inflammatory response in the brain that leads to long-term neurological complications, according to new research from Brazil. In a mouse model, these chronic effects could be partially alleviated by blocking the pro-inflammatory cytokine tumour necrosis factor (TNF).

"During the 2015 ZIKV epidemics in the Americas, a causal relationship between microcephaly in newborns and in utero exposure to the virus was established," explains study leader Julia Clarke. "However, even when no malformation is detectable at birth, babies might still develop motor impairment, seizures and postnatal-onset microcephaly."

To further explore the long-term consequences of early-life ZIKV infection, the researchers infected mouse pups with ZIKV at postnatal day 3 and tracked the development of the animals into adulthood. For the first time, replication of ZIKV was detected in the brain beyond the acute phase of infection. ZIKV replication was accompanied by an inflammatory response, which was characterized by upregulation of various pro-inflammatory mediators, including TNF.

Soon after ZIKV infection, the mice developed spontaneous epileptic seizures, which eventually resolved, although an increased susceptibility to chemically induced seizures persisted into later life. The infected adult mice also showed motor and cognitive impairments and reduced sociability. Systemic treatment with the anti-TNF monoclonal antibody infliximab from the time of ZIKV infection until postnatal day 12 reduced the frequency of spontaneous seizures, but had no effect on the motor or behavioural symptoms.