impeded the production of nitric oxide by the brain vasculature, needed for the response of vessel walls to metabolic needs.[5] Although a role for hypoxia was not clear, nitric oxide deficiency in these salt-fed mice was related to microtubule tau dysfunction and instability. With reversal of this deficiency, both tau dysfunction and cognitive impairment were resolved. These data provide an alternative mechanism for linking vascular disease and dementia-related proteinopathies.

Given vascular contributions to dementia, one would be remiss to not include the report of the SPRINT MIND trial among the most important publications of 2019.[6] The SPRINT MIND trial evaluated the effect of intensive blood pressure control on the risk of dementia. The trial was stopped early because intensive blood pressure control to less than 120 mm Hg was associated with reduced cardiovascular disease and all-cause mortality 5 years later. Analysis of the cognitive endpoints showed that blood pressure of less than 120 mm Hg reduced the risk of mild cognitive impairment and dementia. The study did not meet the primary end point for dementia; however, the number of patients with dementia was small and the study might have been underpowered. Despite these caveats, these data are highly suggestive that intensive blood pressure control in older people is beneficial for cognitive health. Given the prevalence of hypertension in the community, this finding could have a profound effect on the incidence of dementia.

Vascular health interventions, such as adherence to physical activity, a healthy diet, and blood pressure control, are the most compelling means to prevent dementia. Multiple studies have linked brain vascular health either directly or indirectly with cognition. To provide hope to people at high genetic risk, I end by highlighting a study from the UK Biobank.[7] In this large cohort study, the authors found that both unfavourable lifestyles (eg, poor diet and little exercise) and high polygenic risk scores are important risk factors for dementia. However, a favourable lifestyle mitigated the likelihood of dementia among participants with high genetic risk. So, as we leave behind 2019 and enter a new decade with exciting scientific momentum, let's take a moment to make some new year's resolutions for 2020; to pledge our commitment to medical research towards eradicating dementia, and to promote healthy lifestyles for friends, family, patients, and the community.

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I declare no competing interests.

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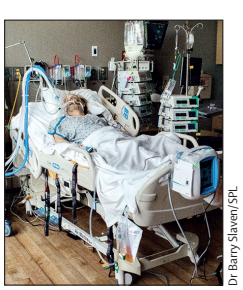
Traumatic brain injury in 2019: databases, biomarkers, and stratified treatment

Although no clinical breakthrough occurred in research on traumatic brain injury in 2019, several substantial advances were made, particularly in large database analyses of patients' characteristics, biomarker monitoring, and stratified treatment of cognitive impairment after traumatic brain injury.

The European CENTER-TBI is one of the most influential ongoing observational cohort studies for traumatic brain injury. 69 research papers have been published from its database so far, covering a broad range of topics, including research methodology, epidemiology, monitoring, outcome prediction, post-traumatic stress disorder, and variation in management between nations. Focusing on the characteristics of patients and care pathways, Steyerberg and colleagues[1] found that patients who presented to European centres in the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core CENTER-TBI study were older (median 50 years [IQR 30–66]; 1254 [28%] of 4509 aged >65 years) than those in previous observational studies. This study also found that Europe has a noticeably higher proportion of old patients than China or India, and that about half of the patients in European centres were admitted to an intensive care unit (ICU), more than a third of whom had mild traumatic brain injury (Glasgow Coma Scale score 13–15).[1] The high proportion of patients in the ICU pathway contrasts with the situation in low-income and middle-income countries, where ICU beds are usually for patients with severe traumatic brain injury. Although CENTER-TBI is well organised, it focuses only on Europe, and more databases in low-income and middle-income countries, international collaborations, and comparative-effectiveness research are essential to achieve a comprehensive view of global practices in the care of these patients.

Diagnostic and prognostic biomarkers for traumatic brain injury have long been keenly sought after. Two US studies on glial fibrillary acidic protein (GFAP) and tau presented new perspectives in this area.[2,3] A multicentre, prospective cohort study of the TRACK-TBI cohort analysed 450 patients with normal CT findings within 24 h after injury.[2] The plasma GFAP concentration in patients with MRI-positive findings (120 patients) was significantly higher than in those with MRI-negative findings. This result shows the value of an early blood GFAP test, which can improve detection of traumatic brain injury and indicates that molecular diagnosis might complement clinical evaluation. Tau also has great potential. Elevated concentrations of phosphorylated tau in plasma can be used as a diagnostic and prognostic biomarker for acute and chronic traumatic brain injury, as shown in a series of clinical trials. Instead of evaluating tau in patients, Alosco and colleagues[3] analysed data from brain donors who had played American football and were diagnosed with chronic traumatic encephalopathy at autopsy. 120 (two-thirds) of 180 patients were found to have had dementia prior to death, and phosphorylated tau was discovered to be one of the neuropathological changes.[3] Therefore, phosphorylated tau might be triggered by a traumatic brain injury and hence cause a pathological cascade towards dementia.

Traumatic brain injury is a heterogeneous condition with a variety of macroscopic modes and underlying pathologies following injury. It is therefore impossible to manage different patients with identical treatment. Screening patients with neuroimaging and then applying stratified intervention could be a promising solution, as shown by two research groups in the UK who explored the effectiveness of a pharmacological treatment or brain stimulation to improve cognition after traumatic brain injury.[4,5] Jenkins and colleagues[4] completed a randomised, double-blind, placebo-controlled, crossover study, which measured dopamine transporters using single photon emission CT and evaluated the effect of methylphenidate (a dopaminergic drug). The cognitive effects of methylphenidate were seen only in patients with low caudal transporter levels. This is an excellent example of precision medicine in traumatic brain injury; identifying patients with a hypodopaminergic state reveals who could benefit from cognitive-enhancing therapy. Li and colleagues[5] evaluated the benefits of transcranial, direct current brain stimulation. Structural MRI was used to assess axonal injury and functional MRI was used to determine the effects of stimulation on cognitive network function. The results showed that white matter structural integrity is necessary for the brain stimulation to have a beneficial effect. Together, these two studies show that precision medicine can involve first a neuroimaging assessment, and then use of this assessment to inform a personalised approach to treatment.

Clinical research on traumatic brain injury in 2019 has advanced our knowledge on key aspects, including patients' characteristics, monitoring, and stratified treatment. All of the studies mentioned were done in high-income countries or regions, and they focused on mild and sports-related traumatic brain injury and the long-term consequences of the injury. Research on severe traumatic brain injury remains controversial and would benefit from further clinical trials. However, several factors contribute to the difficulties in this research area: high-income countries can get funding support and are experienced in clinical trials, but few severely injured patients can be enrolled in these settings, whereas the opposite holds in low-income and middle-income countries. The development of large databases and high-quality clinical research in low-income and middle-income countries, collaborations between high-income countries and low-income and middle-income countries, and comparative effectiveness research studies are thus eagerly anticipated.

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We declare no competing interests.

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Emerging treatments for headache: advances in 2019

Migraine is a highly prevalent neurovascular disorder and the second leading cause of disability worldwide. Cortically spreading depolarisations, which underlie migraine auras, connect to the trigeminovascular system that incites migraine headaches. The role of calcitonin gene-related peptide (CGRP) during the aura is still debated, but is certain in the activation of the trigeminovascular complex. 2019 has been an important year in establishing acute and preventive new therapies for migraine.

To date, triptans are the most prescribed treatment for acute migraine. However, these drugs, which are selective serotonin 5-HT1B/1D agonists and inhibit the release of CGRP, also have vasoconstrictive properties and are not effective in all patients. The development of two novel classes of drugs, gepants (CGRP receptor antagonists) and ditans (serotonin 5-HT1F receptor agonists), for the treatment of acute migraine allows management of patients with cardiovascular comorbidities and those who have severe side-effects or are non-responsive to triptans. For example, lasmiditan, a ditan, was shown effective for acute migraine treatment in a double-blind, randomised, placebo-controlled phase 3 trial.[1] A second phase 3 trial[2] was conducted to replicate findings in patients with acute migraine, including those with cardiovascular risk factors (79% had at least one risk factor). Safety and efficacy findings were consistent with those from the previous phase 3 study. Rimegepant, a gepant, has also been shown to be safe and effective in acute migraine treatment in a double-blind, randomised, placebo-controlled, phase 3 trial comparing an orally disintegrating 75 mg rimegepant tablet with placebo.[3] Based on these positive results, more acute treatment options might be offered in the near future to patients with migraine.

Advances have also been made for episodic cluster headache. Patients with episodic cluster headache (≥1 attacks per day) were randomly assigned to galcanezumab 300 mg, an anti-CGRP antibody, or placebo, administered subcutaneously at baseline and 1 month.[4] Recruitment was halted because too few participants met the eligibility criteria—106 patients were enrolled. The mean reduction in weekly frequency of attacks in weeks 1–3 was 8·7 attacks for galcanezumab compared with 5·2 for placebo (difference 3·5 attacks per week; 95% CI 0·2–6·7; p=0·04). The percentages of responders (≥50% reduction in headache frequency at week 3) were 71% for galcanezumab versus 53% for placebo. Besides injection-site pain for galcanezumab (8%), no differences for adverse events were found. Galcanezumab seems to be an effective preventive treatment option for patients with episodic cluster headache.

Every year about 3% of patients convert from episodic to chronic migraine (≥15 headache days per month, of which ≥8 migraine days). Co-occurrence of chronic migraine with medication overuse triples direct and indirect costs, compared with episodic migraine. Overuse of acute migraine medication is defined as use of triptans on 10 or more days per month for more than 3 months, non-triptan medications such as analgesics or opioids on 15 or more days per month, or use of combination treatments on 10 or more days per month. The current edition of the International Classification of Headache Disorders (ICHD-3)[5] has broadened the