Integrating the characterisation of traumatic brain injury

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Traumatic brain injury (TBI) is a global health concern, as one of the leading causes of disability and death worldwide. The Glasgow Coma Scale (GCS), a widely used grading assessment method, with a history of 51 years,[1] has come under scrutiny for its sole reliance on clinical evaluation. Integrating the characterisation of TBI, both in terms of multidimensional components and temporal progression, has long been anticipated. We are pleased that, in a Policy View published in *The Lancet Neurology*,[2] Geoffrey Manley and colleagues propose a new assessment model for the characterisation of people with acute TBI: the clinical, biomarker, imaging, and modifier (CBI-M) framework.[2] The CBI-M framework comprehensively evaluates patients with TBI according to these four pillars.

The CBI-M framework is a substantial advancement in integrating the characterisation of acute TBI. The main components of the clinical pillar of the CBI-M framework are the GCS and pupillary light reflex, which are crucial indicators in patients with acute TBI. The framework, once again, emphasises the primacy of these indicators. The imaging pillar encompasses all the imaging measures of acute TBI and standardises descriptions. CT and MRI scans reflect intracranial damage objectively and are useful for assessing the severity of the damage and for prognosis. The imaging pillar is also a crucial part of acute TBI assessment. The biomarker pillar, evidence for which has gradually emerged in recent years,[3-5] and the modifier pillar—including various biopsychosocial factors—are integrated for the first time into a comprehensive framework for the evaluation of patients with acute TBI.

The CBI-M framework, however, is not yet ideal. Validity and clinical feasibility are priorities when a pillar for characterisation of acute TBI is used. The biomarker pillar might be applied mainly to the assessment of patients with mild TBI and the sequelae of acute TBI, which has less relevance in guiding acute management for patients with severe TBI, in whom conditions can change rapidly. The biomarker pillar has several limitations. In particular, the detection of biomarkers requires time, and their specificity for the diagnosis of TBI is not high. In these patients, clinically significant changes occur more often in the chronic phase of TBI, and are restricted by detection equipment settings. The use of biomarkers is minimal in low-income and middle-income countries. Similar to the biomarker pillar, the modifier pillar—an individual's biopsychosocial characteristics—can be valuable for predicting outcomes in patients with TBI, but has minimal effect on decision making, particularly during the acute phase of TBI. Another deficiency of the CBI-M framework is that it cannot quantitatively or semi-quantitatively assess the condition of patients with TBI yet. Clinical classification tools need to be operable and follow the principles of simplicity and practicality. To gain recognition and application in countries around the world, the CBI-M framework requires improvement and practical testing through global multicentre, large-scale, prospective cohort studies.

Intracranial pressure, the most crucial physiological index in moderate-to-severe TBI, is unfortunately not considered in the CBI-M framework. The CENTER-TBI China registry study and the SYNAPSE-ICU study have proven that monitoring of intracranial pressure is an important assessment indicator for acute TBI, especially in patients with moderate-to-severe TBI.[6-8] Real-time dynamic changes of intracranial pressure reflects the progress of the intracranial injury, which is irreplaceable in clinical decision making. Additional parameters can further help in monitoring the pathophysiological changes in the brain after TBI, such as cerebral perfusion pressure and the pressure reactivity index for cerebrovascular autoregulation. Based on validity and clinical feasibility, we suggest that the clinical and imaging pillars of the CBI-M framework are recommended as essential pillars. Intracranial pressure monitoring should be conducted in specific patients, if possible, and be eventually incorporated into the CBI-M framework for characterisation of acute TBI. The biomarkers and modifier pillars might not be of equal importance to the clinical and imaging pillars in the evaluation of acute TBI.

This new framework for evaluating and classifying TBI is of considerable value, and underscores the growing potential—in the era of artificial intelligence—to develop a model that integrates future characterisations of TBI. Such a model might enable the convergence of multiple domains of assessment, including clinical presentation, imaging,

pathophysiology, laboratory data, and patient-specific characteristics. It will also enable the integration of key temporal elements such as disease staging, intervention thresholds, risk prediction, and prognosis. A more comprehensive and operational framework is anticipated—one that might substantially enhance the clinical care of patients with TBI.

We declare no competing interests.

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The future of gene therapy for Parkinson's disease

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The burden of Parkinson's disease is increasing inexorably worldwide. Although this trend mirrors that of other neurodegenerative disorders, its relatively high prevalence and potential responsiveness to biological interventions has positioned Parkinson's disease as a research model for the application of gene and cellular therapeutics. A Personal View by Graham Winston and colleagues[1] offers a timely and succinct overview of gene therapy approaches tested for Parkinson's disease, highlighting both progress and challenges, including the pivot to therapies targeting disease pathogenesis rather than restoration of dopaminergic innervation.

The approaches based on circuit restoration—including those that have used adeno-associated virus–glutamic acid decarboxylase (*AAV–GAD*), *AAV–*aromatic-L-amino-acid decarboxylase (*AADC*), and lentiviral vector expressing tyrosine hydroxylase, AADC, or GTP cyclohydrolase (*Lenti–TH–AADC–GTPCH1*)—derive from our understanding of the motor circuit dysregulation that occurs as endogenous dopamine concentrations fall with disease progression, primarily impacting the basal ganglia and its connections.[2] As such, gene therapies can be used either to change the subthalamic nucleus into an inhibitory output structure using *AAV–GAD*, or to re-establish dopamine supplies at striatal nerve terminals with either *AAV–AADC* or *Lenti–TH–AADC–GTPCH1*. The *AAV–GAD* trials were distinct because of their methodological rigor, as they used randomised controlled designs with sham procedures and sophisticated neuroimaging analyses that try to assess circuit reconstruction.[3] Similarly, the *AAV–AADC* and tri-cistronic lentiviral studies showed promising dose-dependent improvements, while also underscoring both the overall safety of the approach and the crucial importance of precise delivery techniques and comprehensive coverage of the target structure in the brain.[4,5]

Despite their promise, these gene therapies face competition from established treatments such as deep brain stimulation (DBS) and dopaminergic pump therapies. Both available technologies also aim to correct circuit dysfunction, but each approach has recognised limitations. DBS involves invasive neurosurgery with devices placed and left in the CNS, with the associated risks, including infections and device failure through lead fractures. Pump therapies, although being less invasive (placed under the skin or directly into the bowel), are still liable to local complications, and their systemic route of administration can cause off-target side-effects. By contrast, gene therapies offer an attractive alternative—a single-administration treatment, centrally delivered, with no indwelling devices left in situ, and with the potential to normalise circuit