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Should plasma GFAP guide the management of patients with traumatic brain injury and a negative CT scan?

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The ability to accurately diagnose the severity of traumatic brain injury (TBI) to establish the consequent need for treatment still eludes modern emergency care systems. Every year, millions of patients worldwide present to emergency departments after head injury,[1] most with debilitating TBI symptoms including impaired consciousness and cognition, amnesia, vomiting, and headache. Currently, the sole standard diagnostic tool is the CT brain scan, which accurately detects TBI in the small minority of patients requiring neurosurgery or neurocritical care for life-threatening injury.[1] However, the CT brain scan is negative in more than 90% of patients with TBI symptoms,[2] leading to uncertainty as to the extent of TBI and likely need for further treatment. The role of MRI after a negative CT finding is currently unclear and not part of routine care in conscious patients (without neurological signs).[1] Adding a routine MRI scan to the pathway of all CT-negative patients (before discharge from the emergency department) could be prohibitively expensive, because an additional stay of some hours or a ward admission would occur.

In children and adults (aged <65 years) injured by high-energy mechanisms, such as motor vehicle collisions and sport, these presenting symptoms could be reasonably attributed to TBI after a negative CT scan, but the recovery trajectory and advice on return to work, participation in sport, and driving is not currently based on precise assessment of TBI severity. The presenting conscious level and duration of amnesia do not provide a reliable guide as to who is at risk of developing disabling post-concussion symptoms.[3] In patients with low-energy falls causing loss of consciousness or amnesia, the diagnostic challenge is greater still, because TBI symptoms can be contiguous with those of intoxication or pre-existing illness causing falls.[4]

Most patients with a negative CT scan are discharged from emergency departments with safety net advice to revisit emergency departments or seek primary care if their post-injury symptoms are disabling. The numbers of CT-negative patients are deemed too great for routine follow-up.[1] However, up to 60% of these patients with so-called mild TBI have clinically significant depression at 10 weeks post injury.[3] It would undoubtedly be cost-effective to have a biomarker of the severity of TBI when the CT scan is negative, because this could direct the need for follow-up clinics, early rehabilitation, and the use of MRI for better injury characterisation, and facilitate advice on return to contact sports.

An analysis of the TRACK-TBI study, reported by John Yue and colleagues[5] in *The Lancet Neurology,* addresses these diagnostic and therapeutic uncertainties; an accurate blood biomarker for TBI in patients with a negative CT scan could be transformative. Glial fibrillary acidic protein (GFAP) is attractive in this regard; it is a specific marker of astrocyte injury. In 2018, the US Food and Drug Administration licensed its use to guide the initial need for CT scan in patients with suspected TBI.[6]

The TRACK-TBI Investigators did a rigorous study of 1234 patients in US trauma centres receiving head CT scan for investigation of TBI whose conscious level was full or minimally impaired (Glasgow Coma Scale score 13–15). 450 of the 794 patients with TBI and negative head CT scans completed follow-up with a head MRI scan. This cohort mainly comprised young people (mean age 36 years) injured by high-energy mechanisms. A quarter (120 [27%]) of these patients had positive findings on MRI scan—most of these (65 [54%]) showing traumatic axonal injury. GFAP concentration at 9–16 h post injury discriminated well between patients with MRI-positive

findings and patients with MRI-negative findings (area under the receiver operating characteristic curve 0·852, 95% CI 0·781–0·923).

These results are promising but, as the investigators acknowledge, are some distance from suggesting that GFAP assays should become part of current emergency department management of patients with TBI and negative CT scans. The clinical significance of the positive MRI findings is unknown; data on patient symptom severity at 2 weeks or later follow-up were not reported in the study. If the frequencies of disabling concussion symptoms do not differ in the MRI-positive and MRI-negative cohorts during follow-up, it is hard to argue that either GFAP or the MRI scans are providing key information to guide further management. Nearly half of the TRACK-TBI patients with negative CT scans did not have MRI as part of their follow-up, and because their characteristics are not reported, it is difficult to assess the potential for selection bias. The frequency of self-reported previous TBI was 9% higher in the MRI-positive cohort than in the MRI-negative cohort. The GFAP assay performed best at 9–16 h post injury and blood sampling occurred at a mean of 12 h after injury. Worldwide, many patients with TBI will have had a negative CT brain scan and been discharged from the emergency department before the period of optimal performance of GFAP in this study.

These issues are all shortcomings, but not necessarily fatal flaws. Through the International Initiative for Traumatic Brain Injury Research, the EU-funded Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study has used a similar observational approach for the detailed assessment of European patients with TBI.[7] If these findings from the TRACK-TBI study can be replicated—and their clinical significance demonstrated—then TBI characterisation with GFAP could lead to improved patient outcomes.

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Do we have equipoise when it comes to how we treat active multiple sclerosis?

The management and treatment of multiple sclerosis has been transformed by disease-modifying therapies (DMTs). The clinical effectiveness of the injectable DMTs interferon beta and glatiramer acetate are relatively modest.[1] However, emerging real-life data show clear inflection points in 2000 and 2006 in terms of patients diagnosed in these more recent periods after reaching or surviving longer to to an Expanded Disability Status Score (EDSS) of 6 (ie, needing a walking stick to walk 100 m). In a cohort study in Italy,[2] patients diagnosed with multiple sclerosis in 1991–95 had a similar likelihood of reaching an EDSS of 6 compared with patients diagnosed in 1980–90 and 1996–2000. However, the hazard ratio of progression to EDSS 6 was reduced by 37% in patients diagnosed in 2001–05 and by 46% in patients diagnosed in 2006–10;[2] these latest epochs were characterised by the wide use of the injectables and the introduction of the first highly active DMTs natalizumab and mitoxantrone.

Efficacy or relative efficacy of individual DMTs becomes somewhat less important than the average efficacy of

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