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Damaged: Elevated GFAP and UCH-L1 as the Black Flag of Brain Injury

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Despite recent advances in neurologic prognostication after cardiac arrest, particularly using neuroimaging and fluid-based biomarkers, there remains a persistent need for objective, accurate indicators of long-term prognosis. In this issue of *Resuscitation*, Ebner and colleagues evaluated the utility of serum biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) for prediction of 6-month neurologic outcome after out of hospital cardiac arrest (OHCA) as measured by the Cerebral Performance Scale (CPC)[6]. For reference, the investigators compared the performance of GFAP and UCH-L1 to that of neuron-specific enolase (NSE). NSE is an enzyme involved in cerebral glycolytic energy metabolism; an elevated level of NSE is a well-established marker of poor prognosis after cardiac arrest.[1] The authors observed that the best model of CPC score at 6 months incorporate levels of GFAP and UCH-L1, which performed better than each of the three biomarkers alone. The addition of clinical parameters further improved the GFAP+UCH-L1 model. While the combination of UCH-L1+GFAP outperformed NSE at 24 hours, performance was similar amongst the markers at later timepoints (48 and 72 hours). These findings suggest that a combined UCH-L1+GFAP assay could improve early prognostication in patients with cardiac arrest compared to NSE alone [6].

For almost two decades, NSE has been a well-established and reliable surrogate marker for poor long-term outcome,[2] inside or outside the context of therapeutic hypothermia.[3] However, NSE has some notable limitations; levels are influenced by hemolysis, and NSE can be elevated from production in other tissues including neuroendocrine tumors.[4,5] Moreover, NSE is incompletely commercially available with turnaround times up to one week, leading to limited clinical utility in the US. Thus, there is room for additional blood-based biomarkers, especially markers that are highly predictive, stable, commercially accessible, and that can be measured early after injury. This paper by Ebner and colleagues is exceptional work as it interrogates a high-quality clinical trial dataset to determine the utility of GFAP and UCHL1, which are increasingly recognized protein biomarkers for prognosis after neurologic injury.[6] The authors also offer cut-points for each marker that can now be validated in future studies.

The combined prognostic power of these damage-associated proteins of neuronal injury (UCH-L1) and glial injury(GFAP) echo observations made in traumatic brain injury (TBI) and stroke.[7] The combined levels of UCHL-1 and GFAP have diagnostic and prognostic

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utility in TBI, proving particularly useful in the prediction of CT lesions in mild TBI.[8,9] In patients with moderate-severe TBI, GFAP has demonstrated robust capacity for predicting the presence of CT abnormalities[10,11] as well as poor clinical outcome.[12,13] Other studies have also supported the use of UCH-L1 for mortality prediction in this population.[14,15] As was observed in the present study, models combining clinical data with serum levels of UCH-L1 and GFAP have been shown to further improve prognostic capacity.[13,15,16] These analogous observations support the validity of measuring central nervous system-specific cellular injury as a surrogate for prognosis, regardless of pathway to that cellular injury (hypoxemia, ischemia, mechanical injury, etc.)

In order to integrate testing of GFAP and UCH-L1 into the clinical practice of prognostication in OHCA, several steps remain. First, the cut-offs proposed here must be validated in an independent sample interrogating their sensitivity and specificity. Prognostic algorithms incorporating clinical information, serum biomarkers, and likely neuroimaging parameters must be trialed. Additionally, we still lack markers of good prognosis in comatose OHCA survivors. While a number of gaps remain, we are likely correct in assuming that elevations of GFAP and UCH-L1 in the appropriate clinical setting do indeed herald the black flag of brain injury and poor outcome.

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