Neurocrit Care (2020) 33:35–36
https://doi.org/10.1007/s12028-020-00942-2

NEUROCRITICAL CARE SOCIETY

INVITED EDITORIAL COMMENTARY

Serum Glial Fibrillary Acidic Protein in Acute Stroke

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Until now, serum biomarkers of brain injury have not had a role in the critical care management of acute stroke. This is due in part to biology; proteins spilled after brain or spinal cord injury are not immediately released from damaged tissues, and when they are must make their way into the bloodstream, crossing the blood–brain barrier or leaching out through the glymphatic system. This limits their utility as ultra-early biomarkers to help with triage or early treatment decisions, since most peak in serum at 24–72 h after an injury. Serum biomarkers additionally tend to be nonspecific, describing severity but not the immediate cause of an injury. What is the use of a serum biomarker when neuroimaging immediately shows the size and location of a stroke or distinguishes ischemic from hemorrhagic lesions with nearly 100% accuracy?

And yet, the prospect of accurate and early serum biomarkers remains tantalizing. Biomarkers could help neurointensivists determine severity of injury, could be used to predict responsiveness to treatment, assess tissue viability, identify ongoing tissue injury, support or speed-up the diagnostic workup, help us better understand pathophysiology, identify treatment targets or guide therapy, act as intermediate endpoints for pilot studies, or aid in prognostication. The more sensitive and specific these biomarkers are, the more they contribute to accurate therapies; the faster they rise and become detectable, the more useful they are in clinical practice—when accompanied by a rapid and accurate test.

In the central nervous system, glial fibrillary acidic protein (GFAP) is found in cytoskeletal filaments of astrocytes and Schwann cells—it has a role in maintaining cytoskeletal shape, motility, and structure, is involved in intracellular signaling and in cellular repair, and helps maintain the integrity of the blood–brain barrier. Unlike most proteins, it rises quickly in the serum after intracerebral hemorrhage (ICH) [1] and may be able to accurately distinguish ICH from acute ischemic stroke (AIS) [2, 3], though high levels can also occur in Parkinson's disease, glioblastoma multiforme, subarachnoid hemorrhage, traumatic brain injury, and bacterial meningitis [4, 5]. It is believed that the acute mechanical disruption of astroglia is responsible for the acute rise in GFAP in patients with ICH, while tissue necrosis occurs more slowly after infarction [5].

In the BE FAST III study, serum levels of GFAP and ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) were evaluated using a new commercial assay at about 130 min after ictus in 251 patients with stroke or stroke mimics in the pre-hospital and emergency department environment. In this ultra-early period, UCH-L1 levels were unhelpful, but mean levels of GFAP were roughly 20 times higher in ICH than ischemic stroke. The AUC for an optimal ROC curve created to establish cutoff values was 0.86 at a 72 ng/L, yielding sensitivity of 75% and specificity of 84%. At a cutoff of 149 ng/L, the specificity for ICH rose to 95%. These are meaningful differences, though the authors are correct to point out various potential weaknesses—such as that patients with intraventricular hemorrhage may have normal GFAP levels (they had none in their cohort), and that small ICH had GFAP levels in the range of patients with ischemic stroke. Absolute separation between ICH and AIS was not present, but at the extremes of GFAP levels, the discrimination was excellent [6].

These results require extensive validation and some clinical experience before we understand how the biomarker functions in practice, but it is easy to imagine

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The original article can be found online at https://doi.org/10.1007/s12028-020-00931-5.

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how GFAP might be used in the future. A very low value might rule out ICH in patients at risk, like anticoagulated or post-tPA patients with headaches, and stable levels might obviate the need for follow-up neuroimaging after ICH or traumatic brain injury (TBI) [7]. If the test were adapted to a rapid bedside assay, it could be used in the pre-hospital environment to triage patients to ultra-early hemostatic therapy, a variation on the FACT trials of recombinant human factor VIIa [8, 9]. Given the recent demonstration of the utility of tranexamic acid in the TBI population [10], early hemostatic therapy may be ready for a comeback in another series of trials, and GFAP could have a role.

Serum biomarkers of brain injury are making their way into routine clinical practice [11, 12], and GFAP for ICH and TBI is a good early candidate. Look out for commercial availability of the test, and for rapid assays, and consider how they might be used to individualize care for your patients, improve efficiency, or select optimal patients for clinical trials.

Funding
None.

Publisher's Note

Published online: 5 March 2020

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