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ARTICLE OF THE MONTH

Biomarkers of Traumatic Injury are Transported from Brain to Blood Via the Glymphatic System

Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, Deane R, Nedergaard M.
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In this May issue of the SNACC Article of the Month, we explore a neuroscience paper which has potentially drastic ramifications for monitoring the extent of TBI and its response to current therapies. For the heart, we have such serum biomarkers as troponin and CK-MB, but for the brain, serum biomarkers of injury have been elusive. Much of this has to do with the fact that transport of injury markers from CSF to the serum is not well understood. The glymphatic system (via cervical lymphatics) is purported to be a vehicle by which such markers might make their way to the bloodstream. The glymphatic system, however, is poorly understood, and entities which may affect it are even less well understood. To shed light on this interesting topic and delve into this article, we have recruited Monica Vavilala, MD, to provide expert commentary. Monica is certainly an expert on TBI, a former SNACC President, and an accomplished researcher in this field (among others). We hope you will enjoy this edition of the SNACC Article of the Month, we thank you for your continued support of this SNACC initiative, and we hope you will chime in on this and previous topics by clicking on the ***SNACC LinkedIn Feed***.

~John F. Bebawy, MD

Commentary

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Traumatic brain injury (TBI) is a major global public health problem. Research to reduce the TBI burden spans multiple domains from basic science to community based participatory research where reintegration of TBI patients and improving functional outcomes are the goals. Despite the vast amount of work being done in these areas, however, some fundamental questions remain regarding what happens to the brain after injury. This has proven to be a very challenging question to answer. For example, we are not clear on optimal blood pressure parameters, whether 100% oxygen benefits neurons, and what levels of glycemic control are desirable. Moreover, we aren't clear on flow: metabolism characteristics and how to detect or stratify TBI severity with high sensitivity and specificity. The latter is proving particularly challenging in the world of mild TBI or concussion where biomarkers remain evasive. Yet, we think that there should be a biomarker of TBI that we can detect in the blood.

Despite millions of dollars of expenses, serum biomarkers such as S 100B and NSE remain research tools; perhaps because it is not particularly clear as to how proteins extravasating from neurons or glial cells end up in the systemic circulation. In fact, as a medical student I don't recall us ever reading about this topic or about the possibility of a brain lymphatic system. The systemic circulation, however, was a different story where lymphatic pathways are better defined.

In this report, Plog and colleagues examined the contribution of the glymphatic system in transport of TBI biomarkers to the peripheral blood. The work is based on recent observations of CSF movement through the recently characterized glymphatic pathway which transports biomarkers to blood via the cervical lymphatics without disrupting the blood brain barrier. The investigators manipulated the following: (1) AQP4 deletion, (2) cisterna magna cisternotomy, (3) acetazolamide treatment, and (4) sleep deprivation, based on their roles in altering glymphatic flow. The main findings are that clinically relevant manipulation of glymphatic activity, including sleep deprivation and cisternotomy, suppressed or eliminated TBI-induced increases in serum S100, GFAP, and neuron specific enolase. Interestingly, although the four mechanisms of glymphatic suppression result in differing degrees of inhibited radiotracer clearance, decreases in serum biomarker levels occurred to an equal extent, perhaps due to a floor effect of glymphatic suppression.

Although previous work has demonstrated that glymphatic CSF-ISF exchange drives the removal of exogenous molecules, including albumin, amyloid, dextrans, and paramagnetic contrast agents from the interstitial space of the brain, this work is exciting in particular because it shows for the first time, evidence of this pathway playing a critical role in the clearance of endogenously produced TBI protein biomarkers from the CNS to the peripheral blood. Future studies should consider the glymphatic pathway when examining the role of TBI biomarkers.