REVOLUTIONARY DIAGNOSTICS – NONTRADITIONAL APPROACHES FOR DEVELOPING BREAKTHROUGH CAPABILITIES AGAINST EMERGING THREATS

Detection Of Biomarkers Of Neurological Injury For Emerging Viral Threats

Darci Smith Naval Medical Research Center, Biological Defense Research Directorate **Heather Poeck-Goux** Naval Medical Research Center **Linwood Johnson** Naval Medical Research Center **Kevin Schully** Naval Medical Research Center **Amy Vittor** University of Florida **Ronald Hayes** Banyan Biomarkers

Infection by neurotropic viruses and the resulting immune response are a significant cause of morbidity and mortality worldwide, which can range in severity from mild cognitive impairment to permanent central nervous system (CNS) damage and death. Encephalitic alphaviruses of military and public health concern include Venezuelan and eastern equine encephalitis viruses (VEEV and EEEV; Alphavirus; Togaviridae), which are mosquito-borne viruses in the Americas that cause CNS disease in humans and equids. Injury to the CNS is an important determinant of poor outcome and tools to predict this outcome are lacking. Neurons are the primary target cells of encephalitic alphaviruses where viral cytopathology plays a major role in CNS dysfunction. A number of proteins are released following cell death, such as ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP). GFAP and UCH-L1 are proteins that when detected in serum or plasma, signal astrocyte and neuronal injury, respectively. These neuromarkers of CNS tissue injury could serve as biomarkers to assess injury severity, monitor disease progression, direct treatment, and as reliable end-points to help develop novel medical countermeasures. Recent advances in the use of blood-based biomarkers for acute diagnosis of brain injury, especially traumatic brain injury (TBI), have provided a firm scientific foundation for expanding the biomarker technology to brain damage caused by other CNS pathologies to include viral encephalitis. The first FDA approved blood test for brain injury was recently approved and was developed by Banyan Biomarkers to detect serum levels of GFAP and UCH-L1 to aid in the diagnosis of mild TBI. A large number of studies of blood biomarkers of acute brain injuries such as TBI, stroke and cardiac arrest in a variety of species including humans have revealed similar profiles of blood biomarker release, suggesting that the same proteins could also detect brain injury resulting from viral encephalitis or other infectious diseases. However, it is unknown if these neuromarkers can be detected in human cases or animal models of viral encephalitis. Here we analyzed serum samples from non-human primates (NHP) infected with VEEV or EEEV to assess for the presence of these neuromarkers. We observed an increase in GFAP and UCH-L1 in NHPs that were infected with EEEV and succumbed from encephalitis, which was in contrast to VEEV infected NHPs that survived infection. Additionally, we evaluated the ability to detect these blood-based biomarkers for other infectious diseases. We analyzed human serum or plasma samples from hospitalized patients with severe coronavirus disease (COVID-19) and patients with encephalitis of unknown origin. Higher levels of UCH-L1 and GFAP were detected in severe COVID-19 cases where many of these patients had signs of neurological impairment. Furthermore, higher levels of UCH-L1 and GFAP were detected in patients diagnosed with CNS infection. Collectively, our results suggest that these blood-based biomarkers may be a good indicator for brain injury resulting from viral infection. Detection of these biomarkers of neurological injury will enhance diagnostic capabilities for CNS infections and help protect the Warfighter from emerging neurotropic viral diseases.

Approved for public release; distribution is unlimited.