The role of Inflammation in the pathophysiology of Post-traumatic brain injury symptomatology: The Post-Traumatic Injury Syndrome (PTIS).

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Abstract: Despite advances in both prevention and treatment, traumatic brain injury (TBI) remains one of the most burdensome diseases; 2% of the US population currently lives with disabilities resulting from TBI. Complex neurochemistry regulates neuronal activity throughout the brain where cell biological, electrical, and neurotransmitter systems enable neural networks to process and drive the entire spectrum of cognition, behavior, and motor functions. Synchronized cooperation amongst distinct cells and interconnected neural circuits rely upon hundreds, if not thousands, of unique molecular interactions. Even single molecule dysfunctions can be disrupting to neural circuit activity, leading to neurological pathology. Recent advances in the understanding of inflammation and its impact on the pathophysiology of trauma have increased the interest in inflammation as a possible mediator for precipitation of neuropsychiatric conditions. Inflammation, precipitated by neurotrauma, is a heterogeneous process that can involve protein-chemicals classified as cytokines, leukotrienes, chemokines, and interleukins, all of which can lead to activation of microglia. Microglial cells resident in the central nervous system react to injury within minutes, and become chronically activated promulgating neuroinflammation and oxidative stress which can persist for 17 years post injury. Coinciding with the development of neuroinflammation, driven specifically by IL-1β, TNF-α, and NFkB, is the onset of mood and cognitive impairment. More recently, the presence of autoantibodies targeting the ion-channels or neuronal receptors including N-methyl-D-aspartate receptor (NMDA-R), voltage gated potassium channel complex (VGKC-complex), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), γ-aminobutyric acid receptor (GABA-R) and dopamine receptor (DR) have been associated with causing neurological and major neuropsychiatric disorders: psychotic, major depression, autism spectrum, obsessive-compulsive and attention-deficit/hyperactivity disorders. The customary clinical approach to trauma related neuropsychiatric disorders has been the stacking of psychotropic medications. Unfortunately, it has become evident that this approach has limitations due to numerous side effects and the lack of inflammatory control.

1. Holly E. Hinson, MD, Depts. of Neurology and Neurocritical Care, Oregon Health and Science University, Portland, Oregon Clinical evidence of inflammation driving secondary brain injury: A systematic review. J Trauma Acute Care Surg. 2015 January; 78(1): 184–191.
2. Koshinaga M, Katayama Y, Fukushima M, et al. Rapid and wide- spread microglial activation induced by traumatic brain injury in rat brain slices. J Neurotrauma 2000; 17:185–192.
3. Gehrmann J. Microglia: a sensor to threats in the nervous system? Res Virol 1996; 147:79–88.
4. David J. Loane and Kimberly R. Byrnes. Role of Microglia in Neurotrauma. The Journal of the American Society for Experimental Neurotherapeutics. Dept of Anesthesiology & Center for Shock, Trauma and Anesthesiology Research (STAR), National Study Center for Trauma and EMS, U. of Maryland School of Medicine, Baltimore, Maryland 21201; and Dept. of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814.
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6. Heidi A. Jurgens and Rodney W. Johnson, Dysregulated Neuronal-Microglial Cross-Talk during Aging, Stress and Inflammation. Neuroscience Program, University of Illinois, Urbana IL 61801. Integrative Immunology and Behavior Program, University of Illinois, Urbana IL 61801, Dept of Animal Sciences, University of Illinois, Urbana IL 61801
7. Carolin Hoffmann, Shenghua Zong, Marina Mané-Damas, Peter Molenaar, Mario Losen and Pilar Martinez-Martinez. Autoantibodies in Neuropsychiatric Disorders. Division Neurosciences, School for Mental Health and Neurosciences, Maastricht University, 6200 MD Maastricht, The Netherlands;