EDITORIAL

Outcome of Hemorrhagic Stroke: Host Immune Response can Be a Prediction Tool!

Prashant Nasa

Keywords: Acute brain injury, Assessment, Biomarkers, Hemorrhage subarachnoid, Intracerebral hemorrhage, Leukocytes, Patient outcome, White blood cells.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24095

Stroke is among the leading causes of death or disability in adults. In the last 10 years, there has been a worldwide decrease in stroke incidence, prevalence, and mortality. However, the disability-adjusted life years and mortality have increased in absolute numbers, especially in developing countries.[1] Hemorrhagic stroke accounting for 10–30% of all cerebrovascular events is catastrophic and has considerable morbidity and mortality. Inflammation and host immune response play a pivotal role in the pathophysiology of hemorrhagic stroke. The inciting hemorrhage mobilizes and activates microglia, astrocytes, macrophages, and T-lymphocytes, resulting in neuroinflammation and vicious progression of secondary brain injury. This involves a multitude of inflammatory mediators like cytokines {Interleukin (IL)-1β, tumor necrosis factor (TNF)-α}, chemokines (nuclear factor-κB), and free radicals. These inflammatory mediators, along with cell death products, cause propagation of neuroinflammation by activation, recruitment, and migration of the Leukocytes. The resultant effect contributes to the disruption of blood–brain barrier (BBB), cerebral edema, and neuronal death.[2]

Substantial evidence accumulated in the last two decades suggested a systemic effect of stroke involving multiple organ systems. The host immune system is an integral part of the systemic effect of the stroke. Dysregulated host immune response to stroke can have divergent manifestations, systemic inflammation to immunosuppression, and can impact outcome.[3] The pathogenesis of brain–body cross-talk in stroke and related immune dysregulation is well established for acute ischemic stroke. However, there is a paucity of data on brain–body cross-talk in hemorrhagic stroke. The activation of the sympathetic nervous system–hypothalamic-pituitary-adrenal (SNS-HPA) axis and resultant catecholamine surge is the initial connection between the central and peripheral immune system. Spleen is a crucial organ in brain–body cross-talk. The SNS-HPA axis activation causes splenic contraction and spleen-independent immune dysregulation and immune paralysis (Fig. 1). The downregulation of peripheral nervous system is another mechanism for splenic contraction and activation of peripheral immune system. Finally, the immune system may be directly activated via brain antigens through the disrupted BBB or CNS lymphatics. There is a free exchange of cytokines like IL-6, IL-1β, TNF-α, C-motif chemokine ligand (CCL)2, and blood cells between the brain and blood through a disrupted BBB. Neutrophil infiltration and release of inflammatory mediators at ischemic parenchymal site propagate tissue injury. The precise mechanism of splenic contraction in hemorrhagic stroke is not known.[3]

Department of Critical Care Medicine, NMC Specialty Hospital, Dubai, United Arab Emirates

Corresponding Author: Prashant Nasa, Department of Critical Care Medicine, NMC Specialty Hospital, Dubai, United Arab Emirates, Phone: +97 1501425022, e-mail: dr.prashantnasa@hotmail.com

How to cite this article: Nasa P. Outcome of Hemorrhagic Stroke: Host Immune Response can Be a Prediction Tool! Indian J Crit Care Med 2022;26(1):2–4.

Source of support: Nil

Conflict of interest: None

The stroke–spleen–peripheral immune system cross-talk can impact the outcome of the acute ischemic stroke and probably in hemorrhagic stroke. The body–brain cross-talk is being explored lately for prediction of disease progression, clinical outcomes, and novel therapeutic options for hemorrhagic stroke.[2,3] The cellular and molecular biomarkers to predict clinical outcomes of hemorrhagic stroke are a long ongoing research.

Peripheral Blood Cells and Hemorrhagic Stroke

The brain–body cross-talk in stroke may cause immune dysregulation and immune paralysis (increasing the risk of infection); through various mechanisms, including recruitment of Leukocytes and decrease in lymphocytes.[4] Peripheral blood cells like Leukocytes, lymphocytes, monocytes, and platelets are surrogates of systemic inflammation and have been studied to predict complications and outcomes of stroke. Divergent results were reported in retrospective studies on total leukocyte count and clinical outcomes in intracerebral hemorrhage (ICH).[5,6] However, a recent meta-analysis of 19 studies and 6,417 patients showed baseline leukocytosis was significantly associated with worse short-term (OR = 1.2; 95% CI, 1.05–1.38), long-term (OR = 1.12; 95% CI, 1.04–1.20), and overall functional outcome (OR = 1.13; 95% CI, 1.05–1.21) in ICH.[7] In another meta-analysis of 13 studies (wide heterogeneity of included studies), leukocytosis was associated with poor outcomes (OR = 1.86; 95% CI, 1.46–2.36) in subarachnoid hemorrhage.[8]

Individual blood cells like lymphocytes and monocytes have also been studied as a prognostic marker in ICH. In a large retrospective observational study, nearly one fourth (27.3%) of patients with ICH had lymphopenia on admission (LOA). LOA was

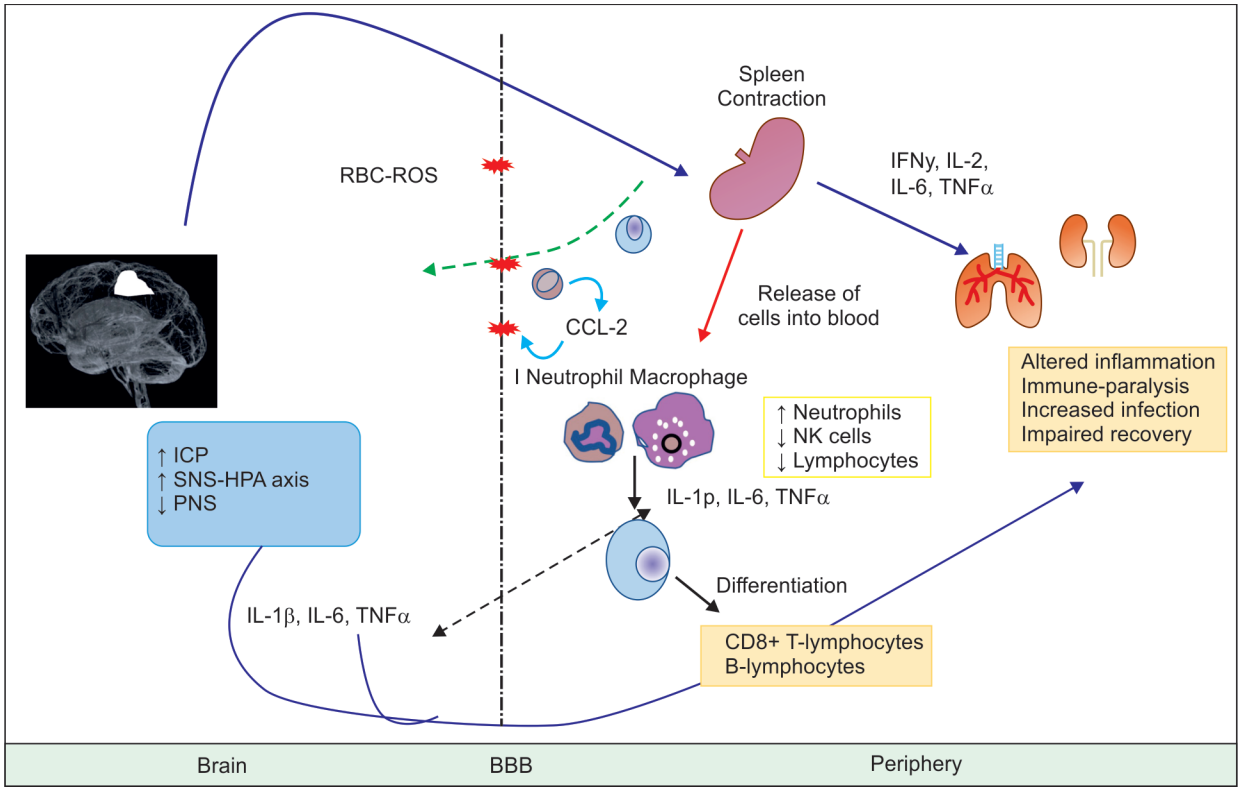

Fig. 1: Peripheral immune response to hemorrhagic stroke. ICP, intracranial pressure; SNS-HPA axis, sympathetic nervous system–hypothalmic-pitutary-adrenal; PNS, peripheral nervous system; RBC-ROS, red blood cells-reactive oxygen species; NK, natural killer; IFN, interferon; TNF, tumor necrosis factor; IL, interleukin; BBB, blood–brain barrier; CCL-2, C-C motif chemokine ligand

independently associated with poor neurological status, large ICH volume, and worse outcomes. Moreover, lymphocytopenia at day 5 had an even more substantial impact on the outcome than LOA.[9] Unlike neutrophil infiltration and expansion of infarct area, the role of lymphocytes in the pathogenesis of stroke remains controversial.[4] Monoctyosis on admission was also independently associated with higher 30-day mortality with ICH.[10]

Neutrophil to Lymphocyte Ratio

Peripheral blood neutrophil to lymphocyte ratio (NLR) is a surrogate marker of both innate (neutrophils) and adaptive (lymphocytes) immune response. NLR has been studied widely to predict severity or outcomes in various diseases, including stroke. Despite various studies on acute ischemic stroke, data on hemorrhagic stroke are currently meagre. In this issue of the journal, Thazhathuveedu et al. studied the role of NLR in a prospective cohort study of hemorrhagic stroke patients. Higher mean NLR was associated with poor functional outcome at day 90 in hemorrhagic stroke, with a sensitivity and specificity of 84 and 66.3%, respectively.[11]

In a recent meta-analysis of 41 studies on stroke and 11 studies on hemorrhagic stroke, elevated NLR was associated with significantly increased mortality (eight studies, OR = 1.23; 95% CI, 1.09–1.39) and poor outcome in acute hemorrhagic stroke (seven studies, OR = 1.11; 95% CI, 1.03–1.20). The cut-off value of NLR varied between different studies.[12]

The linkage of elevated NLR to poor prognosis is postulated through excessive inflammation and immunosuppression. The inflammation after hemorrhage is a natural body response. However, hyperinflammation may be counterproductive and may cause secondary brain injury. On the contrary, immunosuppression (due to catecholamines surge and lymphopenia) increases the risk of secondary infection after stroke.[12,13]

Molecular Biomarkers and Hemorrhagic Stroke

Various molecular biomarkers like matrix metallopeptidase 9 (MMP-9), TNF-α, IL-11, and CRP have been studied in ICH.[14,15] However, elevations of these inflammatory mediators in ICH represent either a causal association to disease severity and outcome or are directly involved in the secondary brain injury processes is an ongoing debate.[2]

In conclusion, there are various gaps in the understanding of brain–body cross-talk during a hemorrhagic stroke. Emerging data suggest that peripheral immune cells like NLR are inexpensive biomarkers to predict outcomes. Future research should incorporate these biomarkers into existent prediction models of clinical outcomes and explore novel therapeutic targets.

Orcid

Prashant Nasa https://orcid.org/0000-0003-1948-4060

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