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Mini Review

Impact of Albumin and Fibrinogen on Early Brain Injury

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ABSTRACT

Cerebral Aneurysmal Subarachnoid Hemorrhage (aSAH) is a major cause of hemorrhagic stroke worldwide, with an annual incidence of 9 per 100,000 people, accounting for approximately 85% of Subarachnoid Hemorrhages (SAH). Once an aneurysm ruptures, there is a high risk of early patient mortality, emphasizing the need for prompt treatment. Surgical intervention can successfully treat a ruptured aneurysm and reduce the risk of rebleeding; however, 20% to 30% of patients may experience focal neurological or cognitive impairments. In patients with subarachnoid hemorrhage, early hypoalbuminemia is an independent predictor of hospital death. Albumin levels after subarachnoid hemorrhage have a time-dependent connection with death, with a stronger correlation with early mortality than with late mortality. Fibrinogen, spilling through the compromised blood-brain barrier, reaches the brain parenchyma. Procoagulants cause it to change into insoluble fibrin at the site of arterial rupture, where it deposits in the brain parenchyma. Through a number of mechanisms, fibrinogen both initiates and contributes to the inflammatory response of the post-bleeding neurological system. Fibrinogen increases the release of reactive oxygen species and the production of pro-inflammatory cytokines and chemokines after attaching to receptors on microglial/macrophage cells. Additionally, it can cause microglial cells to undergo M1-like metamorphosis, which exacerbates the inflammatory response of the nervous system and worsens disruption of the blood-brain barrier and brain injury. The Albumin/Fibrinogen Ratio (AFR), a novel inflammatory biomarker, has been shown to have considerable prognostic value in a range of illnesses, including cancer and myocardial infarction. In individuals with acute ischemic stroke, a lower AFR was found to be independently associated with a higher likelihood of hemorrhagic transformation. Moreover, AFR can indicate the degree of retinal vein blockage. The predictive value of AFR for patients with aSAH is currently unclear. The aim of this study was to examine the link between the admission Hunt-Hess (HH) scale score and 6-month outcomes for patients with aSAH and AFR. One of the main effects of cerebral bleeding is brain edema, which is made worse by the increase in fibrinogen concentration, which, as was previously discussed, disrupts the blood-brain barrier in a number of ways. An overabundance of fibrinogen will impair patients' red blood cells' capacity to deform plastically, accelerate the lysis of red blood cells, and cause hyper coagulation in patients-A condition that increases the risk of secondary coagulation and the fibrinolysis system-as well as delayed cerebral edema.

Keywords: Cerebral aneurysmal subarachnoid hemorrhage; Hemorrhagic stroke; Ruptured aneurysm; Fibrinolysis

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INTRODUCTION

Research indicates that Early Brain Injury (EBI) may be associated with the prognosis of patients with ruptured aneurysms [1,2]. EBI encompasses pathological and physiological changes within the first 3 days after onset, including increased intracranial pressure, blood-brain barrier disruption, cascading inflammatory reactions, oxidative stress responses, and apoptosis [3]. The above studies suggest that levels of Albumin/Fibrinogen Ratio (AFR) and the Hunt-Hess (HH) score at admission are correlated with the 6-month prognosis of aSAH patients. AFR, as an inflammatory biomarker, may predict prognosis and could be linked to the pathophysiological changes involved in or related to EBI. This article will separately elucidate the roles of albumin and fibrinogen in patients with aneurysmal hemorrhage or cerebral hemorrhage and discuss the potential of AFR as a predictive factor.

LITERATURE REVIEW

Impact of albumin on early brain injury

Albumin is synthesized by the liver in the form of pre albumin and constitutes approximately 40% to 60% of the total plasma protein. The normal range of albumin in plasma is 35 to 55 g/L. It plays crucial roles in the body: (1) Albumin elevates the colloid osmotic pressure of plasma, facilitating the absorption of fluid from the interstitial spaces, thereby improving tissue and organ perfusion [4]. Changes in colloid osmotic pressure also promote the synthesis of serum albumin [5]. (2) Albumin can bind to inflammatory substances, reducing or eliminating their toxicity and maintaining the stability of the body's internal environment. (3) Albumin helps maintain cellular metabolism by increasing the transport of ketones and neurotransmitters, thereby protecting nerve cells [6]. (4) Albumin possesses significant antioxidant properties, clearing the activity of free radicals, improving microcirculation, reducing leukocyte adhesion, and producing anti-inflammatory effects [7]. (5) Albumin contributes to the repair of damage, coordinates hemodynamics, and maintains the stability of the blood-brain barrier. After the rupture of an arterial aneurysm, the extravasated blood components activates microglial cells, and it is found in a rat model of subarachnoid hemorrhage that albumin may bind to microglial cells, inhibiting receptors through these cells to alleviate the inflammatory response [8]. Early hypoalbuminemia is an independent predictor of hospital mortality in subarachnoid hemorrhage patients. It is more closely related to early mortality than to late mortality, indicating a time-dependent relationship with albumin levels after subarachnoid hemorrhage [9].

Furthermore, patients with Intracerebral Hemorrhage (ICH) and concurrent hypoalbuminemia are more likely to experience adverse functional outcomes [10]. The use of human albumin in the treatment of ICH patients can promote hematoma absorption and improve neurological function. This mechanism may be achieved by reducing post-bleeding inflammatory reactions and inhibiting oxidative stress responses. Additionally, albumin can inhibit the activity of thrombin, enhance antithrombin activity, promote fibrinolysis, and stimulate phagocyte proliferation, improving microcirculation and thus enhancing patients' neurological function and long-term prognosis [11].

Impact of fibrinogen on early brain injury

Disruption of cerebral vascular integrity is a critical factor in the pathological mechanism of aneurysmal rupture and subsequent neural damage. The key factors in blood-brain barrier disruption are the activation of inflammation, including the activation of microglial cells, upregulation of various inflammatory mediators, and increased blood-brain barrier permeability due to the destruction of tight junction proteins [12,13]. Fibrinogen, leaking through the damaged blood-brain barrier, enters the brain parenchyma. At the site of vascular rupture, it is converted into insoluble fibrin under the action of procoagulants, depositing in the brain parenchyma. Fibrinogen induces and participates in the post-bleeding neural system's inflammatory response through various pathways. After binding to receptors on microglial/macrophage cells, fibrinogen stimulates the secretion of pro-inflammatory cytokines and chemokines, as well as the release of reactive oxygen species. It can also induce M1-like transformation in microglial cells, exacerbating the neural system's inflammatory response and further worsening blood-brain barrier disruption and brain damage [14].

Fibrinogen can bind to intercellular adhesion molecule-1, increasing endothelial cell layer and blood vessel permeability through extracellular signal-regulated kinase 1/2 signaling, activating matrix metalloproteinase-9, further degrading tight junctions between endothelial cells, disrupting the integrity of the endothelial cell layer, and ultimately causing blood-brain barrier breakdown [15]. This exacerbates secondary brain damage. The post-bleeding neural system's inflammatory response, along with blood components such as iron, hemoglobin, fibrinogen, can promote oxidative stress reactions, further aggravating secondary brain damage [16].

The role of Early Brain Injury (EBI) in delayed neurological dysfunction of aSAH patients should not be disregarded, as it has become an emerging focus in research on Acute Stroke Hemorrhage (aSAH). EBI is closely linked to the incidence of Delayed Cerebral Ischemia (DCI), the occurrence of disability, and mortality following Asah [3]. Early test results may be able to predict a patient's prognosis and aid in the early diagnosis of EBI. Consequently, investigating specificity measurements as potential predictive risk factors for aSAH is still crucial. In addition to cerebral vasospasm and DCI, immune-related inflammation of the central nervous system is a major pathophysiological factor in EBI following a SAH. A novel inflammatory biomarker called the Albumin/Fibrinogen Ratio (AFR) has been revealed to have significant predictive value in a number of disorders, including myocardial infarction and cancer. A decreased AFR was found to be independently linked to an increased risk of hemorrhagic transformation in patients with acute ischemic stroke. Furthermore, the degree of retinal vein obstruction can be predicted by AFR. For patients with aSAH, the prognostic usefulness of AFR is still unknown. The

purpose of this study was to look at the relationship between 6-month outcomes for patients with aSAH and AFR in addition to the admission Hunt-Hess (HH) scale score.

DISCUSSION

Brain edema is a major complication of cerebral hemorrhage, and the increase in fibrinogen concentration, as mentioned earlier, exacerbates blood-brain barrier disruption through multiple pathways. Excessive fibrinogen level will affect the plastic deformation ability of red blood cells in patients, increase the destruction of red blood cells, and lead to hypercoagulation of blood in patients, which is prone to secondary coagulation and fibrinolysis system, and further lead to the occurrence of delayed cerebral edema. Research indicates that fibrinogen can induce the expression of pro-inflammatory cytokine IL-6 and oxidative damage in neurons, ultimately leading to neuronal death [17]. Numerous studies have shown that fibrinogen inhibits neural system repair by regulating central nervous system injury and disease-induced inflammatory responses and growth factor receptor signaling. Using hirudin to inhibit fibrin formation, degrading locally damaged fibrinogen with batroxobin, and using the monoclonal antibody 5B8 targeting the fibrinogen γ377-395 epitope may inhibit neural inflammation and oxidative stress, reducing axonal injury and potentially aiding long-term recovery after cerebral hemorrhage [18,19].

CONCLUSION

In summary, albumin has a positive effect on improving the prognosis of patients with ruptured aneurysmal bleeding, while fibrinogen exacerbates secondary brain damage in these patients. Presenting them as a ratio, such as AFR, as a predictive indicator for the prognosis of patients with ruptured aneurysmal bleeding may amplify the roles of both, resulting in positive outcomes in our study. However, the level of albumin cannot be infinitely amplified or reduced, and an appropriate level of albumin combined with AFR may give more meaningful results to this research.

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