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Hepatic responses following acute ischemic stroke: A clinical research update

Honglian Duan[1], Xiaokun Geng[1,2,3], Yuchuan Ding[3]

Abstract:

Acute ischemic stroke (AIS) not only affects the brain but also has significant implications for peripheral organs through neuroendocrine regulation. This reciprocal relationship influences overall brain function and stroke prognosis. Recent research has highlighted the importance of poststroke liver changes in determining patient outcomes. In our previous study, we investigated the relationship between stroke and liver function. Our findings revealed that the prognostic impact of stress-induced hyperglycemia in patients undergoing acute endovascular treatment for acute large vessel occlusion is closely related to their preexisting diabetes status. We found that the liver contributes to stress hyperglycemia after AIS by increasing hepatic gluconeogenesis and decreasing hepatic insulin sensitivity. These changes are detrimental to the brain, particularly in patients without diabetes. Furthermore, we examined the role of bilirubin, a byproduct of hepatic hemoglobin metabolism, in stroke pathophysiology. Our results demonstrated that blood bilirubin levels can serve as predictors of stroke severity and may hold therapeutic potential for reducing oxidative stress-induced stroke injury in patients with mild stroke. These results underscore the potential role of the liver in the oxidative stress response following AIS, paving the way for further investigation into liver-targeted therapeutic strategies to improve stroke prognosis and patient outcomes.

Keywords:

Bilirubin, brain–liver interaction, glucose metabolism, liver enzyme

[1]Department of Neurology, Beijing Luhe Hospital, Capital Medical University, [2]Department of Neurology, Luhe Institute of Neuroscience, Capital Medical University, Beijing, China, [3]Department of Neurosurgery, School of Medicine, Wayne State University, Detroit, MI, USA

Address for correspondence:
Prof. Xiaokun Geng, Department of Neurology, Beijing Luhe Hospital, Capital Medical University, No. 82 Xinhua South Road, Tongzhou, Beijing 101149, China. E-mail: xgeng@ccmu.edu.cn
Prof. Yuchuan Ding, Department of Neurosurgery, School of Medicine, Wayne State University, 550 E Canfield, Detroit, MI 48201, USA. E-mail: yding@med.wayne.edu

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With the accelerated aging of the population, ischemic stroke has become a heavy disease burden worldwide.[1] Acute brain ischemia leads to a series of alterations in the immune system, the hypothalamic–pituitary–adrenal axis, and the autonomic nervous system, which negatively affect peripheral organs and contribute to ischemic brain injury development.[2,3] Emerging research highlights a bidirectional communication between the brain and liver, as evidenced by changes in hepatic glucose metabolism, bilirubin, and liver enzyme levels in the early stages of an ischemic stroke, which subsequently influence stroke prognosis. To uncover novel stroke treatments, recent clinical studies have focused on the relationship between poststroke liver serological markers and cerebral infarction severity and prognosis, exploring the therapeutic potential of "treating the liver to reduce brain damage."

The liver plays a crucial role in maintaining energy and glucose metabolism, with stress hyperglycemia concurring in around one-third of individuals after an acute ischemic stroke (AIS).[4-7] This stress hyperglycemia stems from an inflammatory hepatic pathway that promotes hepatic gluconeogenesis and reduces insulin sensitivity, resulting from the arousal of autonomic nervous system and the hypothalamic–pituitary axis during AIS.[8-10] Stress-induced hyperglycemia peaks within 24 h and normalizes by the 3rd day.[11] This hyperglycemia can impair cognition, predict larger ischemic areas, increase mortality risk,[12] and worsen clinical outcomes.[12,13] The glucose-to-glycated hemoglobin ratio (GAR) is an index that reflects the change of glucose

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after AIS, eliminating the influence of the previous blood sugar level. Higher GAR values indicate more severe stress-related hyperglycemia[14-17] and have been linked to poor outcomes in patients undergoing mechanical thrombectomy (MT) and intravenous thrombolysis (IVT).[12,18-22] However, stroke patients without diabetes mellitus (DM) have higher morbidity and mortality because of stress-related hyperglycemia than stroke patients with combined DM and have a poorer prognosis,[23-26] including patients who received IVT.[25]

Our recent study investigated the potential of stress-induced hyperglycemia as a prognostic indicator in patients with AIS who underwent emergent endovascular treatment (EVT). In patients without DM, we discovered that GAR was independently associated with poor outcomes after 3 months. However, this correlation was not observed in patients with DM. The prognostic role of stress-induced hyperglycemia in acute large vessel occlusion patients undergoing EVT was influenced by their premorbid diabetes status. In diabetic patients, poor prognosis was not independently associated with stress-induced hyperglycemia. This lack of association could be due to the long-term effects of persistent elevated blood sugar levels and adaptive changes in the stress response of diabetic patients following acute ischemic brain injury.[27,28]

Bilirubin, a powerful intrinsic antioxidant, is generated as a byproduct of hepatic heme metabolism. Research supports serum bilirubin's involvement in antioxidant activities, allowing it to play a crucial role in preventing stroke development.[29-31] However, elevated serum bilirubin levels after AIS can be detrimental. Serum bilirubin levels following AIS can serve as valuable markers reflecting illness severity. Both total bilirubin (Tbil) and direct bilirubin (Dbil) after stroke onset are associated with increased stroke severity, as assessed by the National Institutes of Health Stroke Scale.[32,33] Moreover, within 48 h after MT, admission serum bilirubin levels serve as independent predictors of symptomatic cerebral hemorrhage and hemorrhagic conversion.[34] The relationship between serum bilirubin and short-term clinical outcomes remains controversial.[35-37] Elevated serum bilirubin levels are associated with negative outcomes in patients following stroke onset, potentially reflecting the severity of the initial oxidative damage. In the pathophysiology of brain injury, excessive oxidative stress is critical in contributing to both functional and structural brain damage. While high serum bilirubin levels can be beneficial for oxidative stress-induced stroke, excessive concentrations become toxic. Patients with AIS and high bilirubin levels exhibit larger cerebral infarcts, more pronounced cerebral edema, more severe reperfusion injury, and worse functional prognosis than those with low bilirubin levels.[38] Our team discovered that in all AIS patients, elevated levels of Tbil and Dbil within 48 h of symptom onset may independently indicate stroke severity at both admission and discharge. Interestingly, for patients with mild stroke, increased bilirubin levels following AIS are associated with a favorable outcome.[39] Our investigation implies that moderately rather than excessive serum bilirubin levels may offer therapeutic effects against oxidative stress-induced stroke injury. We presume that the anti-oxidative stress effect of bilirubin may play a role in patients with mild stroke, suggesting a potential contribution to oxidative stress response in AIS from the liver. Altered bilirubin levels may be a clinical phenomenon of the hepatic response in patients with AIS and have prognostic value, especially in patients with mild stroke.

Other liver function indices, such as aspartate aminotransferase (AST) and alanine transaminase (ALT) are glutamate-regulated enzymes that reduce glutamate levels, the most abundant excitatory neurotransmitter in the central nervous system, which has multiple physiological functions and act as a neurotoxin in pathological states. Elevated levels of ALT and AST are linked to lower infarct sizes and improved outcomes in patients experiencing the acute stage of ischemic stroke.[40-42]

Clinical studies have demonstrated an interaction between the liver and the brain. Stroke can induce functional or metabolic changes in the liver, elevating liver enzymes, or blood glucose levels, which in turn can either protect or exacerbate brain damage and influence stroke severity and outcome. Our current work on poststroke liver function and metabolism alterations underscores the impact of peripheral organ changes on stroke outcomes from a clinical perspective.

In conclusion, we highlight the complex and bidirectional communication between the brain and the liver following an ischemic stroke. The liver plays a significant role in maintaining energy and glucose metabolism and alterations in liver function can directly impact stroke outcomes. Recent findings emphasize the importance of understanding the relationship between poststroke liver serological markers and stroke severity, as well as prognosis. Serum bilirubin levels, in particular, have shown potential for therapeutic intervention against oxidative stress-induced stroke injury, provided that they remain within a moderately elevated range. In addition, further investigation into the role of liver function indices, such as ALT and AST, could lead to a better understanding of their impact on stroke outcomes. As we continue our research, we aim to integrate the treatment of primary brain injury with interventions

targeting secondary systemic complications. By tailoring our approach to individual patient characteristics, we hope to optimize stroke outcomes and advance the field of stroke treatment. Ultimately, a comprehensive understanding of the brain–liver interaction could open new avenues for stroke management and improve patient care, potentially reducing the global burden of ischemic stroke.

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Conflicts of interest

Prof. Yuchuan Ding is an Associate Editor, Prof. Xiaokun Geng is an Editorial Board member of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

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