Inflammatory Process in Hepatic Encephalopathy: The Role of Interleukin-18

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Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities associated in patients with liver dysfunction and/or portosystemic shunting. It is one of the most serious complication of cirrhosis. HE is associated with increase hospitalization, increase in health cost, and mortality of cirrhosis patients. Approximately 30-45% of cirrhosis patients will develop HE and it is the most common cause of hospitalization in decompensated cirrhosis patients. Cirrhosis patients who had HE had 1-year survival probability of 42% and 3-year probability of 23%.[1]

HE comprises a complex, multifactorial, mechanisms resulting in functional impairment of neuronal cell. For many years, ammonia was considered as the main role of the pathogenesis of HE. However, many studies showed that blood ammonia levels may not correlate with the degree of HE suggesting more compounds were involved. In recent years, many agents emerge as a part of HE pathogenesis such as deposition manganese in the basal ganglia, benzodiazepine-like compounds, microbiota, aromatic amino acids, and also inflammatory cytokines.[1]

Many evidences showed that inflammation plays important role in the development of HE. Astrocytes and microglia are capable to produce proinflammatory cytokines as a response to inflammatory state in cirrhosis patients.[2] These cytokines will increase blood-brain barrier permeability for ammonia and its passage into astrocytes.[3] It has been long documented that the levels of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukins (ILs) were increase in decompensated cirrhotic patients.[4] In 1995, Izumi et al had shown that interleukin (IL)-6 was correlated with fulminant hepatic failure and chronic HE.[5] Since then, multiple interleukins were identified to be associated with HE including IL-18.[6]

IL-18 is a proinflammatory cytokine, previously describe as interferon γ-inducing factor, involved in activation and differentiation of various T cell populations.[7] IL-18 show proinflammatory properties such as increase in cell-adhesion molecules, nitric oxide synthesis, and chemokine production.[8] Other than induce the inflammatory state, IL-18 may induce HE by disturbed intestinal permeability and mucus production by goblet cells resulted in dysbiosis and increase of plasma endotoxin.[7,10]

Recent study by Anton et al showed that mean serum of IL-18 levels were higher in the cirrhosis patients compared to healthy controls (688.5 ± 674.3 pg/mL vs. 163.9 ± 100 pg/mL; $p = 0.01$). In this study, IL-18 was significantly correlated with HE ($r = 0.85$; $p < 0.05$). More importantly, IL-18 levels were significantly different between the severity grade of HE.[11] These evidences show possibilities to utilize IL-18 for diagnosis and management HE in the future.

REFERENCES

1. Elwir S, Rahimi RS. Hepatic encephalopathy: an update on the pathophysiology and therapeutic options**.** J Clin Transl Hepatol 2017;5:142–51.
2. Haussinger D, Schiliess F. Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. Neurochem Int 2005;47:64-70.
3. DeVries HE, Bloom-Roosemalen MC, Van OM, DeBoer AG, Van Berkel TJ, Breimer DD, et al. The influence of cytokines on the integrity od the blood-brain barrier in vitro. J Neuroimmunol 1996;64:37-43.
4. Tilg H, Wilmer A, Vogel W, Herold M, Nölchen B, Judmaier G, et al. Serum levels of cytokines in chronic liver diseases. Gastroenterology 1992;103:264-74.
5. Izumi S, Hughes RD, Langley PG, Pernambuco JR, Williams R. Acute phase response after liver transplantation for fulminant hepatic failure and cirrhosis. Transpl Int 1995;8:340–5.
6. Mueser UF, Schimdt OI, Oberholzer A, Bu¨hrer C, Stahel PF. IL-18: a key player in neuroinflammation and neurodegeneration? Elsevier 2005;28:487-93.
7. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. Annu Rev Immunol 2001;19:423-74.
8. Kaplanski G. Interleukin-18: biological properties and roles in disease pathogenesis. Immunol Rev 2018;281:138–53.
9. Jain L, Sharma BC, Sharma P, Srivastava S, Agrawal A, Sarin SK. Serum endotoxin and inflammatory mediators in patients with cirrhosis and hepatic encephalopathy. Elsevier 2012;44:1027-31.

10. Hanck C, Manigold T, Böcker U, Kurimoto M, Kölbel C, Singer M, et al. Gene expression of Interleukin-18 in unstimulated peripheral blood mononuclear cells of patients with alcoholic cirrhosis. Gut 2001;49:106-11.
11. Komala A, Mustika S, Pratomo B. Overview of serum Interleukin-18 (IL-18) levels in liver cirrhosis patients and their correlation to hepatic encephalopathy. Indones J Gastroenterol Hepatol Dig Endosc 2018;19:67-73.