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

Andri Sanityoso Sulaiman
Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine
Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

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