

Proinflammatory Cytokines Correlate with Diffusion Tensor Imaging Derived Metrics in Patients with Acute and Acute-on-Chronic Liver Failure

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Introduction: Acute liver failure (ALF) is a potentially reversible, often sudden, persistent and progressive liver dysfunction in the absence of pre-existing liver disease, characterized by occurrence of encephalopathy within 4 weeks (1) while acute on-chronic liver (ACLF) is liver failure developing in patients with previously well-compensated chronic liver disease following an acute precipitating event (2). Hepatic encephalopathy (HE) is the neuropsychiatric manifestation of liver disease ranging from minimal alteration in mental state to deep coma. Proinflammatory cytokines and hyperammonia are considered as main factors responsible for the pathogenesis of HE (3). It is reported that cerebral edema (CE) is a major complication of ALF as well as ACLF. CE is predominantly cytotoxic in ALF (4) while it is a mixture of cytotoxic and interstitial in ACLF (2). It is reported that proinflammatory cytokines alter the hemodynamic property of brain by inducing the nitric oxide synthesis, while ammonia is detoxified by astrocytes to glutamine, resulting in synergism of action of these two different mediators in the development of CE (5). MRI studies, including ¹H-MR spectroscopy, diffusion-weighted and diffusion tensor imaging have been studied in ALF and ACLF in humans (2, 4) as well as animal model (6). However no study is available that explores the relationship between proinflammatory cytokines and imaging & ¹H-MR spectroscopy indices in patients with ALF and ACLF. The aim of this study was to look for the correlation of DTI derived metrics and ¹H-MR spectroscopy derived metabolites with serum proinflammatory molecules in both these forms of liver failure.

Patients and Methods: Fourteen patients with ALF (mean age 34±11years), 17 with ACLF (mean age 42±12 years) and 8 controls were included in this study. The study protocol was approved by the institutional ethics committee and written informed consent obtained from caregiver. ALF was diagnosed in patients, who developed hepatic encephalopathy within 4 weeks of the development of jaundice and had no clinical and radiological evidence of cirrhosis (Tandon BN). ACLF was diagnosed when there was evidence of acute hepatitis, defined as an abrupt rise (over < 4 weeks) in serum bilirubin to ≥10 mg% and ALT to ≥5 times of normal (≥200 IU/L), developing in a patient with clinical, biochemical or ultrasonographic evidence of liver cirrhosis. Blood ammonia, serum proinflammatory cytokines (IL-6 and TNF-α), conventional MRI, DTI and ¹H-MR spectroscopy were recorded in all patients as well as in controls. DTI and ¹H-MR spectroscopy data acquisition and processing were done as per the previously published study (7). For measurement of ammonia, blood was taken after overnight fasting, and measured by ammonia checker. Serum proinflammatory molecules were quantified by using standard ELISA method from the commercially available kits. Mean diffusivity (MD) and spherical anisotropy (CS) value measured from spectroscopy voxel co-registered with MD and CS map. ¹H-MR Spectroscopy derived metabolites, DTI metrics, blood ammonia and serum proinflammatory cytokines were compared by one-way analysis of variance with Bonferroni multiple comparisons post hoc analysis. For the purpose of correlation Pearson correlation coefficient was used.

Result: On DTI, ALF patients showed significantly increased CS and decreased MD as compared to controls; however ACLF patients showed significantly increased CS along with no significant change in MD values. On ¹H-MR spectroscopy significant increased Glx/Cr with decreased Cho/Cr was common in both conditions, while mIns/Cr significantly decreased only in the ACLF patients. Serum proinflammatory molecules were significantly increased in both conditions as compared to controls; however ALF had insignificantly higher serum proinflammatory molecules than ACLF (Fig.1). A significant positive correlation of CS with IL-6 and TNF-α in ALF while in ACLF, CS correlate only to IL-6. A significant negative correlation was observed between MD values with IL-6 in both conditions. (Fig.2). A significant positive correlation was found between Glx/Cr with IL-6 and TNF-α in both liver failures (Fig.2).

Discussion: Hyperammonemia, inflammation and oxidative stress are considered the major contributors to the pathogenesis of HE. It has been reported that proinflammatory cytokines and hyperammonemia synergistically acts and produces the symptoms of HE and CE (8). The proinflammatory cytokines can activate the synthesis of nitric oxide in the astrocytic cells resulting in vasodilatation and hyper-circulation (8); however ammonia produces osmotic effect and increased water in astrocytic cells resulting in CE. Astrocytic cells form an integral component of blood brain barrier and regulate the cerebral blood flow therefore these cells may be the critical cells interacting between ammonia and inflammation. In a recent study Jiang et al (9) have reported generalized increased in proinflammatory cytokines in animal model of ALF and were associated with microglial activation and brain edema. In this study we observed significantly increased serum proinflammatory cytokines in patients with ALF and ACLF indicates proinflammatory cytokines are present in these patients, consistent with previous study and suggest that these play a role in both type of CE (cytotoxic and interstitial). The change observed on DTI and ¹H-MR spectroscopy in ALF and ACLF are consistent with our previous published study (2, 4). We observed a significant positive correlation of proinflammatory cytokines with DTI derived metrics CS and significant negative correlation with MD value in both form of disease; suggest that these proinflammatory cytokines may contribute in both types CE. A significant positive correlation of Glx/Cr with proinflammatory cytokines suggest that glutamine and proinflammatory cytokines synergistically act and generate the CE.

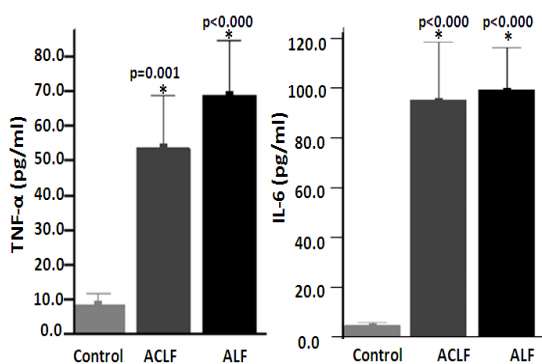


Figure 1 showed the mean±SD of proinflammatory serum cytokines TNF-α and IL-6 levels in controls acute liver failure and acute-on-chronic liver failure patients.

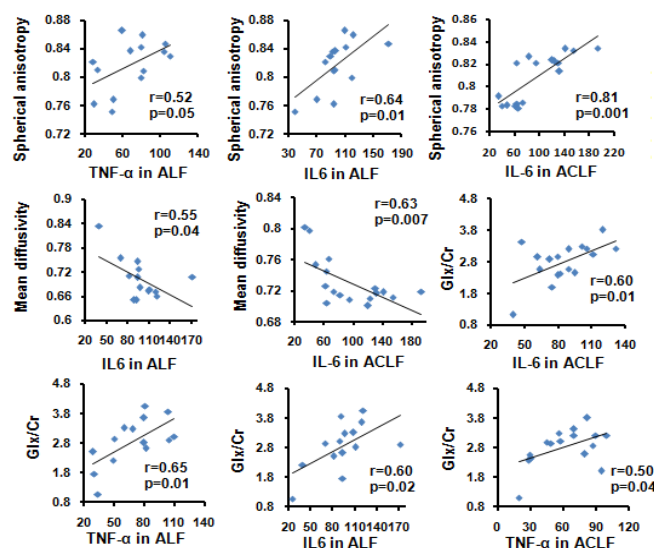


Figure 2 showed correlation of proinflammatory molecules (TNF-α and IL-6) with DTI derived metrics (MD and CS) and ¹H-MR spectroscopy derived metabolite Glx/Cr in patients with ALF and ACLF

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