Characterization of Cerebral Edema in Acute-on-Chronic Liver Failure

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Background and Aims: **The nature of cerebral edema in acute-on-chronic liver failure (ACLF) is not well studied. We aimed to characterize cerebral edema in ACLF using magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI).** ***Methods:*** **Forty-six patients with cirrhosis and acute decompensation were included. Patients were divided into groups A (no cerebral failure, *n* = 39) and B (cerebral failure, *n* = 7). Group A was subdivided into no-ACLF (*n* = 11), grade 1 (*n* = 10), grade 2 (*n* = 9) and grade 3 (*n* = 9) ACLF as per CANONIC study. MRI brain and plasma TNF-alpha, IL-1beta and IL-6 were measured at baseline and 7–10 days after admission. Ten age- and sex-matched healthy controls were also included.** ***Results:*** **Mean diffusivity (MD) values, an MRI marker of water content, progressively increased from controls to no-ACLF to ACLF grade 1, 2 and 3 in group A in frontal white matter (FWM) and basal ganglia ($P < 0.0001$). MD values improved only in survivors on follow-up. MD values correlated with IL-6 levels at baseline. On multivariate analysis MELD score $\geq$28 and MD values (>8 $\times$ 10^{-9} M^2/s) in FWM were independent predictors of 90-day mortality. There was no significant difference in clinical and MRI parameters between group A and B.** ***Conclusion:*** **Cerebral edema increases with severity of ACLF. Correlation between MD values and IL-6 levels suggests pathogenic role of inflammation in cerebral edema. Patients with grade 3 ACLF have cerebral edema irrespective of presence of clinically evident cerebral failure. MELD score and cerebral edema have prognostic significance in ACLF. (J Clin Exp Hepatol 2017;7:190–197)**

ACLF

In chronic liver disease, raised blood ammonia levels cause intracellular accumulation of glutamine which disturbs brain cell volume homeostasis. Subsequently depletion of myoinositol tries to maintain intracellular osmolytes balance and reduces or limits the cellular swelling.[1] This is reflected as low-grade astrocyte swelling which manifests as clinical or minimal hepatic encephalopathy. The conventional magnetic resonance (MR) imaging lacks the sensitivity for detection of mild and diffuse changes in brain water content. However, advanced MRI techniques like magnetization transfer ratio (MTR), diffusion tensor imaging (DTI) and diffusion weighted imaging (DWI) are sensitive to changes in increased brain water content and also help in differentiating the intracellular and extracellular component of brain edema. Magnetization transfer imaging has shown decrease of magnetization transfer ratio (MTR) in normal-appearing white matter and normal-appearing gray matter regions in patients with cirrhosis.[2] MTR and fast fluid attenuation inversion recovery (FLAIR) sequences do point to mild brain edema but are unable to distinguish whether the edema is intracellular or extracellular. DTI assesses different parameters like mean diffusivity (MD), a marker of water movement across cell membranes thereby assessing interstitial edema, and fractional anisotropy (FA), an index of microstructural integrity of normal appearing white matter hence assessing demyelination and axonal loss.[3]

Systemic inflammation is induced by infection and hepatocyte cell death in liver failure. Therefore, systemic and central inflammatory cytokines acting alone or in combination with ammonia result in neuroinflammation. The raised cytokine levels can cross the blood brain barrier directly, cause microglial activation, which further leads to monocyte recruitment and increased cytokine gene expression in brain.[4,5] There is convincing evidence that neuroinflammation has a role in pathogenesis of

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Abbreviations: ACLF: acute-on-chronic liver failure; AIH: autoimmune hepatitis; ALIC: anterior limb of internal capsule; APASL: Asian pacific association for study of liver diseases; AUROC: area under receiver operating characteristic; BG: basal ganglia; BBB: blood–brain barrier; CANONIC: chronic liver failure (CLIF) acute-on-chronic liver failure in cirrhosis; CI: confidence interval; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; CTP: Child–Turcott–Pugh; DTI: diffusion tensor imaging; FA: fractional anisotropy; FLAIR: fluid attenuation inversion recovery; FWM: frontal white matter; HBV: hepatitis B virus; HE: hepatic encephalopathy; IC: internal capsule; IL-1 beta: interleukin 1 beta; IL-6: interleukin 6; MD: mean diffusivity; MELD: model for end-stage liver disease; MRI: magnetic resonance imaging; MTR: magnetization transfer ratio; PLIC: posterior limb of internal capsule; PWM: parietal white matter; ROI: regions of interest; SIRS: systemic inflammatory response syndrome; T1W: T1 weighted; T2W: T2 weighted; TE: echo-time; TR: repetition time; TNF-alpha: tumor necrosis factor-alpha

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encephalopathy in liver failure. The severity of edema seems to differ according to duration of liver failure and degree of hyperammonemia. Chronic liver failure induces low-grade interstitial brain edema and any acute insult resulting in systemic inflammation may cause increased neuroinflammation and resultant encephalopathy.[6]

As per chronic liver failure (CLIF) acute-on-chronic liver failure in cirrhosis (CANONIC) study, presence of organ failure and increased 28-day mortality in patients of cirrhosis with acute decompensation has been used to define acute-on-chronic liver failure (ACLF).[7,8] We have demonstrated that sepsis is the most common cause of acute decompensation in cirrhosis.[9] Cerebral changes, including the degree and type of brain edema, and their pathophysiology, including the role of systemic inflammation, have not been well characterized in ACLF population.

We aimed to study various brain magnetic resonance imaging (MRI) findings [T1 weighted (T1W), T2 weighted (T2W), FLAIR, MTR and DTI] and inflammatory cytokines (TNF-alpha, IL-1beta, IL-6) in patients with different grades of ACLF and explore their role as prognostic indicator(s) of mortality along with other clinical parameters. We also compared clinical and MRI parameters between patients with grade 3 ACLF with and without cerebral failure (presence of grade III/IV hepatic encephalopathy).

METHODS

Study Conduct

The Ethics Committee of Postgraduate Institute of Medical Education and Research (PGIMER), a tertiary level health care center in Chandigarh, India, approved the study (letter no. 1TRG/PG-2012/21508-520 dated 8/11/13). Each subject or their legal representatives gave written informed consent before being included into the study. The guidelines laid down by Indian Council of Medical Research (1994) and Helsinki declarations (modified 1989) were adhered to in all patients in the study. The authors had access to all study data, and reviewed and approved the final manuscript.

Patients

Eligible patients included consecutive inpatients from Department of Hepatology, PGIMER with acute decompensation of cirrhosis, defined as per Moreau et al.[7] Exclusion criteria were as follows: those who refused informed consent, any neurologic diseases such as Alzheimer's disease, Parkinson's disease or stroke, chronic kidney disease, cardiopulmonary disease, pregnancy, contra-indications to MRI, and hepatocellular carcinoma.

Controls

Ten age- and sex-matched healthy subjects [mean age (range)—controls 40.2 (28–58) years, patients 41.6 (24–70) years; male: female—control 9:1, patients 35:4] were also included in study to serve as controls for MTR and DTI and for tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta) and interleukin-6 (IL-6) measurement.

Definitions

Cirrhosis of Liver

The diagnosis of cirrhosis of liver was based on liver biopsy if available or clinical, imaging, laboratory and endoscopic findings.[9]

Acute Decompensation

The CANONIC study criteria were used to define acute decompensation, which included acute development of ascites, hepatic encephalopathy (HE), gastrointestinal bleeding and bacterial infections.[7] Alcohol consumption in last 3 months was considered as active alcoholism.[7]

Acute-on-Chronic Liver Failure

The CLIF-SOFA score was applied to define and grade severity of ACLF based on organ failures.[7] Liver failure was defined as serum bilirubin $\geq$12.0 mg/dL, kidney failure as serum creatinine $\geq$2.0 mg/dL or patient requiring renal replacement therapy, cerebral failure as presence of grade III/IV HE defined by West Haven classification,[10] coagulation failure as international normalized ratio $\geq$2.5 and/or platelet count $\leq$20,000/mm^3, circulatory failure as patient requiring vasopressors to maintain blood pressure and respiratory failure as PaO_2:FiO_2 $\leq$200 or a SpO_2:FiO_2 $\leq$214 or requiring mechanical ventilation. Cerebral failure was defined as presence of grade III/IV hepatic encephalopathy.

Clinical and Laboratory Assessment

Clinical examination included a thorough general physical and systemic examination. Laboratory investigations included hemogram, serum electrolytes, renal and liver function tests and coagulogram. All patients underwent etiological work-up for cirrhosis and acute decompensation. Severity of cirrhosis was determined by Child–Turcotte–Pugh's (CTP) and model for end-stage liver disease (MELD) score. TNF-alpha, IL-1 beta, and IL-6 were measured in plasma using specific enzyme-linked immunosorbent assay kits (RayBiotech, Inc, Norcross, GA) according to manufacturer's protocol. The plate was read at 450 nm. Absorbance was converted to picograms per milliliter using a standard curve prepared with recombinant human TNF-alpha, IL-1 beta and IL-6.

Neuroimaging

Whole brain conventional MR imaging was performed on either a 3.0 Tesla Verio MR scanner (Siemens Medical Solutions, Erlangen, Germany) or on 3.0 Tesla Discovery MR750 scanner (GE medical systems, Milwaukee, USA)