UPDATE IN HEPATIC ENCEPHALOPATHY - PART II

In this issue of the Journal of Clinical and Experimental Hepatology, the reader will find a second series of articles that represent a consolidated effort at clarifying and simplifying our views on pathogenesis, classification and management of hepatic encephalopathy (HE). The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) organized 17th ISHEN Symposium that took place in Gurugram, India from 9th to 11th March 2017 where experts discussed various aspects of HE, from nomenclature to etiology, pathogenesis, classification, diagnosis, treatment and to outcome. The current issue presents the second series of peer reviewed review articles based on their research and clinical experience as a “Special Section: Update in Hepatic Encephalopathy” - Part II.

The experts have discussed new insights in the pathogenesis of HE. Amodio¹ reviews the current diagnosis of HE and the pathophysiological, clinical, prognostic, and treatment implications thereof. The spectrum of HE ranges from mild brain dysfunction, extrapyramidal manifestations, chronic or recurrent presentation, rapidly progressive inhibited or agitated acute confusional state to hepatic coma. The distinction between the patients with cirrhosis between those with and those without acute-on-chronic liver failure (ACLF) is emphasized.² They propose to label HE in ACLF as a type (type ‘D’) separate from type ‘C’ which may require specific diagnostic and treatment procedures that differs from the ones used in patients without ACLF.³ At present, there is no data to suggest that there is any mechanism of HE that is peculiar to ACLF.⁴ As discussed in the previous reviews by Jayakumar and Norenberg⁵ on the role of ammonia in HE and Azhari and Mark Swain⁶ on neuroinflammation, future research on the unique pathophysiology of HE in ACLF will be of keen interest. Lauridsen and Vilstrup⁷ elaborate on the tests to use in minimal hepatic encephalopathy (MHE) and the ability to identify patients who will benefit from anti-HE treatment. Currently the armamentarium of tests include the Portosystemic Hepatic Encephalopathy Score (PHES), the Continuous Reaction Time Test (CRT), the Inhibitory Control Task Test (ICT), The Critical Flicker Frequency Test (CFF), and spectral EEG.⁸ The role of newer app-based tests is also described though these need standardisation and validation as no proper norms exist.⁹ The simple animal naming test, which requires no equipment and simply requires the patient to name as many animals as possible in 60 seconds was recently reported that cirrhotics who were able to name less than 10 animals

had an 80% likelihood of also being classified as having MHE or worse by the PHES.¹⁰

Sheikh and Agarwal¹¹ present an analysis of neurological monitoring in acute liver failure reflecting the pathogenesis of HE, including circulating neurotoxins such as ammonia, systemic and neuro-inflammation, infection and cerebral hyperaemia due to loss of cerebral vascular autoregulation. The HE in ALF is multifactorial and can rapidly progress to cerebral oedema and raised intracranial pressure (ICP), with intracranial hypertension (ICH) (ICP>25 mmHg) predisposing to cerebral herniation and death. Currently available tools to monitor HE in ALF include invasive intracranial pressure monitoring,¹² jugular venous oxygen saturation,^{13,14} transcranial Doppler¹⁵ and optic nerve sheath diameter assessment (ONSD).¹⁶ Near-infrared spectrophotometry, optic nerve ultrasound and serum biomarkers of brain injury are of future interest.

Dam et al¹⁷ present the available evidence on the role of branched chain amino acids (BCAA; leucine, isoleucine and valine) in the management of HE. The ‘Fischer’s ratio’ between BCAA and aromatic amino acids in plasma has been associated with the grade of HE.¹⁸ In the setting of hepatic dysfunction, when the liver fails, this homeostasis is altered and muscle tissue becomes the main alternative organ for ammonia metabolism. BCAAs enhance muscle mass and exert anabolic effects via stimulation of protein synthesis possibly improving the sarcopenia associated with cirrhosis.¹⁹ Nardelli and Riggio et al²⁰ explores the role of radiological interventions in the management of HE. Episodes of HE are usually related to precipitating events, such as infections or gastrointestinal bleeding; or may be acute events on a background of chronic HE, which is refractory to standard medical treatment. Another type of HE should be related to spontaneous or radiological (such as TIPS) portal systemic shunts, that could be restricted or occluded in patients with chronic HE.²¹ Both TIPS reduction and shunt occlusion are radiological procedures, safe and effective to ameliorate neurological symptoms in patients with refractory HE. The specific roles of Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)²² and Plug-Assisted Retrograde Transvenous Obliteration (PARTO) or Coil-Assisted Retrograde Transvenous Occlusion (CARTO) to occlude large spontaneous porto-systemic shunts have been described.²³

Finally, Grover and Ghosh²⁴ review the key elements of delirium tremens (DT) from a psychiatric perspective. The prevalence of DT in general population is <1% and nearly 2% in patients with alcohol dependence.²⁵ DT presents

Corresponding author.

<https://doi.org/10.1016/j.jceh.2018.11.001>

with a symptoms of alcohol withdrawal, delirium with agitation and sometimes hallucinations. The authors discuss the predictive factors²⁶ and clinical evaluation of DT²⁷ including severity of alcohol withdrawal, evaluation of delirium, and screening for underlying medical comorbidities. In addition, the updated dosing protocols of benzodiazepines,²⁸ and second line drugs like phenobarbital, dexmedetomidine, ketamine and propofol have been described which are essential knowledge for the clinician.²⁹

The Editors believe that the resulting compilation of reviews is informative and hope the reader will share this appreciation. The final and Part III compilation will be published in the February 2019 (first) issue of the Journal of Clinical and Experimental Hepatology.

REFERENCES

- Amodio P. Diagnosis and Classification of Hepatic Encephalopathy. *J Clin Exp Hepatol*. 2018;8:432–437.
- Lee GH. Hepatic encephalopathy in acute-on-chronic liver failure. *Hepatol Int*. 2015;9:520–526.
- Cordoba J, Ventura-Cots M, Simon-Talero M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). *J Hepatol*. 2014;60:275–281.
- Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. *J Hepatol*. 2015;62:437–447.
- Jayakumar AR, Norenberg MD. Hyperammonemia in hepatic encephalopathy. *J Clin Exp Hepatol*. 2018;8:272–280.
- Azhari H, Swain M. Role of Peripheral Inflammation in Hepatic Encephalopathy. *J Clin Exp Hepatol*. 2018;8:281–285.
- Lauridsen MM, Vilstrup H. Testing in the Real World Scenario-A Mini Review. *JCEH* 2018. *J Clin Exp Hepatol*. 2018;8:438–440.
- Bajaj JS, Etemadian A, Hafeezullah M, Saeian K. Testing for minimal hepatic encephalopathy in the United States: An AASLD survey. *Hepatology*. 2007;45:833–834.
- Bajaj JS, Heuman DM, Sterling RK, Sanyal AJ, Siddiqui M, Mathew S, et al. Validation of EncephalApp, Smartphone-Based Stroop Test, for the Diagnosis of Covert Hepatic Encephalopathy. *Clin Gastroenterol Hepatol*. 2015;13:e1.1828–e1.1835.
- Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, De Rui M, et al. The animal naming test: An easy tool for the assessment of hepatic encephalopathy. *Hepatology*. 2017;66:198–208. <http://dx.doi.org/10.1002/hep.29146>.
- Sheikh MF, Unni N, Agarwal B. Neurological Monitoring in Acute Liver Failure. *J Clin Exp Hepatol*. 2018;8:441–447.
- Vaquero J, Fontana RJ, Larson AM, Bass NMT, Davern TJ, Shakil AO, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transplantation*. 2005;11:1581–1589.
- Peck M, Wendon J, Sizer E, Auzinger G, Bernal W. Intracranial pressure monitoring in acute liver failure: a review of 10 years experience. *Critical Care*. 2010;14:P542.
- Rajajee V, Fontana RJ, Courey AJ, Patil PG. Protocol based invasive intracranial pressure monitoring in acute liver failure: feasibility, safety and impact on management. *Critical Care*. 2017;21:178.
- Aggarwal S, Brooks DM, Kang Y, Linden PK, Patzer 2nd JF. Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure using transcranial doppler ultrasonography. *Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2008;14:1048–1057.
- Moretti R, Pizzi B, Cassini F, Vivaldi N. Reliability of optic nerve ultrasound for the evaluation of patients with spontaneous intracranial hemorrhage. *Neurocritical Care*. 2009;11:406–410.
- Dam G, Aamann L, Vilstrup H, Gluud LL. The role of Branched Chain Amino Acids in the treatment of hepatic Encephalopathy. *J Clin Exp Hepatol*. 2018;8:448–451.
- Chatauret N, Desjardins P, Zwingmann C, et al. Direct molecular and spectroscopic evidence for increased ammonia removal capacity of skeletal muscle in acute liver failure. *J Hepatol*. 2006;44:1083–1088.
- Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, Vilstrup H. Branched chain amino acids for people with hepatic encephalopathy. *Cochrane Database Syst Rev*. 2017 May;18:5.
- Nardelli S, Gioia S, Ridola L, Riggio O. radiological Intervention for Shunt Related Hepatic Encephalopathy. *J Clin Exp Hepatol*. 2018;8:452–459.
- Simón-Talero M, Roccarina D, Martínez J, et al. Association Between Portosystemic shunts and Increased Complications and Mortality in Patients With Cirrhosis. *Gastroenterology*. 2018 Jan 20. pii: S0016-5085(18)30069-6.
- Mukund A, Rajesh S, Arora A, et al. Efficacy of balloon-occluded retrograde transvenous obliteration of large spontaneous lienorenal shunt in patients with severe recurrent hepatic encephalopathy with foam sclerotherapy: initial experience. *J Vasc Interv Radiol*. 2012;23:1200–1206.
- Lee EW, Saab S, Gomes AS, et al. Coil-assisted retrograde transvenous obliteration (CARTO) for the treatment of portal hypertensive variceal bleeding: preliminary results. *Clin Transl Gastroenterol*. 2014;5:e61.
- Grover S, Ghosh A. Delirium Tremens: Assessment and management. *J Clin Exp Hepatol*. 2018;8:460–470.
- Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med*. 2014;371(22):2109–2113.
- Goodson CM, Clark BJ, Douglas IS. Predictors of severe alcohol withdrawal syndrome: a systematic review and meta-analysis. *Alcohol Clin Exp Res*. 2014;38:2664–2677.
- Moore DT, Fuehrlein BS, Rosenheck RA. Delirium tremens and alcohol withdrawal nationally in the Veterans Health Administration. *Am J Addict*. 2017;26:722–730.
- Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA*. 1997;278:144–151.
- Gold JA, Rimal B, Nolan A, Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. *Crit Care Med*. 2007;35:724–730.

**Madhumita Premkumar, MD, DM,
Radha K. Dhiman, MD, DM, FAMS, FACG, FRCP,
FAASLD ***

Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

E-mail: rkpsdhiman@hotmail.com

*Corresponding author at: Professor, Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India