Scientific advances in hepatic encephalopathy

Hepatic encephalopathy (HE) is a major neuropsychiatric complication of liver failure and continues to be a major clinical problem. This issue of the Indian Journal of Gastroenterology contains reviews of the most recent scientific advances in HE, with contributions from international and national investigators. These topics were presented and discussed at the “Single Theme Conference on Hepatic Encephalopathy” held in Chandigarh October 6, 2000. The text was subsequently revised to make the information up-to-date. This issue includes articles related to HE associated with acute liver failure (type A), with porto-systemic bypass (type B), or with cirrhosis and portal hypertension (type C).

The first two articles by Drs Tandon and Chandy review current nomenclature and methods of quantification of HE. Dr Tandon focuses on the new standardized nomenclature of HE suggested by the Working Party commissioned by the Organisation Mondiale de Gastroenterologie in 1998. A multiaxial definition of HE has been suggested that defines both the types of hepatic abnormality (type A, B or C) and the duration/characteristics of type C HE. The new nomenclature should be helpful in providing standardized definition for future clinical studies and for better outcome measure to report efficacy in therapeutic trials. Dr Chandy’s article highlights the limitations of several methods such as psychometric tests, electroencephalography (EEG) and evoked potentials in the assessment of HE: the West Haven criteria for semiquantitative grading remains the most acceptable. The Glasgow coma scale is also useful for patients in stage III and IV HE.

Dr Mullen provides an overview of recent advances in HE. Dr Butterworth elucidates our current understanding of the pathogenesis of HE. While ammonia remains the leading toxin and plays an important role in the pathogenesis of this syndrome, recent molecular studies demonstrate increased expression of several genes coding for neurotransmitter-related proteins in chronic liver failure. These genes encode for monoamine oxidase-A isoform, neuronal isoform of nitric oxide synthase, and peripheral type benzodiazepine receptor. Activation of these systems can lead to alterations in neurotransmitter systems and cerebral blood flow changes that may be responsible for many clinical manifestations of HE. Therapeutic implications of these findings are yet to be explored.

Drs Sachdev and Duseja review the relationship of various types of porto-systemic shunts with the development of HE. Dr Mullen emphasizes the need to examine the complex interrelationship between portal pressure, portal perfusion and hepatic arterial perfusion in inducing HE after creation of porto-systemic shunts. Patients with non-cirrhotic portal hypertension do not develop HE even after a large variceal bleed. HE develops only when these patients develop liver parenchymal disease or undergo decompressive surgical shunts. It appears that preserved or increased portal pressure protects these patients from developing HE; however, further studies are required to examine this complex inter-relationship.

The articles by Drs Chetri and Choudhuri and Duseja et al describe the role of zinc, manganese and Helicobacter pylori in the pathogenesis of HE. Manganese is neurotoxic, affecting both neuronal and astrocytic integrity. As much as 10-fold increase in manganese concentration in the globus pallidus has been observed in patients with liver cirrhosis with HE, thus warranting a trial with chelation therapy. There are conflicting reports regarding the association between H. pylori and HE. Duseja et al provide a balanced overview of current understanding on this issue. These articles are followed by an overview by Drs Bhatnagar and Majumdar on different animal models of HE.

The next three articles are devoted to minimal hepatic encephalopathy (mHE). The term mHE is preferred over the misleading terms “subclinical” or “latent” that may suggest that the condition is below the threshold of significance. Several issues related to mHE need to be examined in prospective studies; these include (i) the natural history of mHE, (ii) the best approach to diagnose mHE, (iii) the significance of mHE, (iv) the impact of mHE on the quality of life (QOL), and (v) should mHE be treated? In the first article, Dr Singh and coworkers suggest that neuropsychometric and neuropsychological tests remain the tests of choice to diagnose this condition and suggest the use of a combination of psychometric, (at least two of the following: number or figure connection test, NCT or FCT, block design test, or digit symbol test) and neurophysiological tests (P300 auditory evoked potentials or mean dominant frequency of electroencephalography). PSE-syndrome test and critical clicker frequency need further validation before they can be recommended for broader use. There are not many studies on the natural history of mHE. Duseja et al reviewed this aspect and found that the natural history of mHE is not entirely benign and is probably also an independent predictor of survival. Treatment with lactulose, L-ornithine L-aspartate, or dietary manipula-
Son is effective; however, its impact on the natural history and QOL should be studied in larger prospective studies.

Magnetic resonance spectroscopy (MRS) is a unique tool that permits the detection and quantification of certain brain metabolites in vivo. The article by Drs Gupta and Dhiman addresses the utility of magnetic resonance imaging and MRS in HE. H-MRS shows characteristic patterns of an increase in glutamine/glutamate peak and a decrease in the myoinositol and choline signal. Several studies have shown a correlation between MRS findings and psychometry in patients with mHE.

The next section deals with therapeutic aspects of HE. While the current decade has witnessed several advances in the nomenclature and pathogenesis, there is no significant therapeutic breakthrough. With advances in our understanding of the alterations in various neurotransmitters, newer neuropharmacological agents that act directly on the CNS may be available in the near future. Dr Dasarathy provides an insight into the role of gut bacteria in ammoniagenesis and ammonia-lowering therapeutic strategies. Drs Prabhakar and Bhatia elucidate the management of agitation or convulsions in cirrhotic patients with HE. The choice of anticonvulsant and antipsychotic drug is difficult in these patients due to pharmacokinetic and pharmacodynamic derangements in decompensated cirrhosis.

The rest of this issue is devoted to HE associated with acute liver failure (type A). Dr Butterworth provides an overview of the pathophysiology and treatment of cerebral edema. Rapid accumulation of ammonia in the brain and its subsequent detoxification by glutamine synthetase leads to accumulation of glutamine in the astrocyte that results in astrocyte swelling (cytotoxic brain edema). The author describes altered expression of several genes in the brain that code for various proteins responsible for maintenance of cell volume integrity and neurotransmission. L-ornithine L-aspartate appears promising in animal models, and prospective therapeutic trials should be performed in humans. Dr Mukherjee et al discuss the measurement and utility of intracranial pressure monitoring and various therapeutic options for its treatment.

Acute liver failure has a grim prognosis, with survival rate of 15% to 30%. Clinical and biochemical criteria have been devised to select out patients with unfavorable outcome so that liver transplantation can be offered to them. Drs Batra and Acharya highlight the differences between prognostic models devised in Western countries and those devised in India. Two recent studies have shown that serum phosphate levels and arterial lactate concentration may have prognostic value in acetaminophen-related acute liver failure; however, validation studies in patients with ALF of various etiologies from other centers are required.

Only 10%-15% of patients with ALF who need liver transplantation ultimately receive one. Dr Anand provides an excellent overview of various artificial liver support systems that may be useful to bridge the time to transplantation and/or to recover from ALF. Liver transplantation in India is still in its infancy. Drs Minz and Siwash provide the current status of liver transplantation.

Finally, Dr Aggarwal discusses the major causes and the management of HE in pregnancy. Acute viral hepatitis E is common in developing countries and usually has a self-limiting course. However, pregnant women particularly may have a disastrous outcome. The reasons for this are not known. Future studies should be directed to find out the reason for such an unfavorable course among pregnant women.

We hope this issue of the Journal is useful to clinicians and investigators. We would like to thank all authors for their contribution. We also acknowledge the excellent support from the Journal's editorial team, in particular Drs Philip Abraham, Shobha Bhatia, and Rakesh Aggarwal.

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