EDITORIAL

HEPATIC ENCEPHALOPATHY

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Hepatic encephalopathy is a complication of cirrhosis and is not a uniform clinical entity; rather, it encompasses a spectrum of neuropsychiatric disturbances affecting motor function, cognition, personality, and consciousness.[1] Clinical manifestations range from coma to subtle cognitive ab-normalities detectable only on psychometric or neurophysiologic testing. The mild manifestation of hepatic encephalopathy, termed minimal hepatic encephalopathy, is estimated to affect up to 60% of patients with cirrhosis[2] and may seriously impair a patient's daily functioning and quality of life. Psychomotor slowing and deficits in attention, visual perception, and visuoconstructive abilities are key features, whereas fine motor performance is also impaired. Minimal hepatic encephalopathy can render a patient unfit to drive a motor vehicle and is an important predictor of the development of overt hepatic encephalopathy.[2] Hepatic encephalopathy occurs in approximately 30 to 45% of patients with cirrhosis[3] and portends a poor prognosis. Indeed, the probability of transplant-free survival after the first episode of acute hepatic encephalopathy is only 42% at 1 year and 23% at 3 years.[4]

The pathogenesis of hepatic encephalopathy remains incompletely studied, although a cen-tral theme of all current hypotheses is that the accumulation of ammonia, predominantly derived from the intestine, plays a crucial role. Gut flora, especially urease-containing species, such as kleb-siella and proteus species, are an important source of ammonia in humans. The deamination of glutamine in small-intestinal mucosa and, to a lesser extent, renal and muscle synthesis also contribute.[5] In patients with cirrhosis, the accumulation of ammonia results mainly from im-paired hepatic clearance due to hepatocellular fail-ure or portosystemic shunting. Other gut-derived toxins, such as benzodiazepine-like substances, short- and medium-chain fatty acids, phenols, mercaptans, and manganese, may interact with ammonia to exacerbate neurochemical changes.[1] In addition; a synergistic effect of inflammation is likely to be important in causing hepatic en-cephalopathy.[6]

The use of no absorbed disaccharides or antibiotics (alone or in combination) to reduce the colony counts of ammonia-producing gut flora and to decrease the systemic absorption of ammonia from the intestinal lumen forms the main-stay of current guidelines for the management of hepatic encephalopathy that is a complication of cirrhosis. This treatment approach is currently suggested for use while a precipitating event, such as sepsis, gastrointestinal bleeding, renal dysfunction, electrolyte imbalance, or constipation, is being reversed and also when no reversible factor is identified.[5]

Despite the widespread, long-standing clinical impression that such therapy is effective, a critical appraisal of relevant trials published from 1969 to March 2003 concluded that the results of those studies did not meet current standards of evidence-based medicine.[7] This analysis has highlighted the need for better-designed studies that can properly assess the efficacy of traditional therapies. However, such studies are particularly difficult to perform, in view of the confounding factors that must be considered and the necessity to enroll adequate numbers of patients with well-defined disease across the clinical spectrum of hepatic encephalopathy. Further, standardized definitions, assessment tools, and out-come measures are important for obtaining clinically meaningful results.

Substantial rates of treatment failure remain, highlighting the need for additional treatment strategies for this debilitating and potentially life-threatening condition. Further, carefully designed studies are needed to elucidate the role of other approaches to changing the composition of gut flora that currently show promise for the treatment of hepatic encephalopathy, such as the use of probiotics or of prebiotics combined with probiotics. Whether it is of benefit to combine therapies that alter the composition of gut flora with measures designed to both increase the tissue detoxification of ammonia and reduce proinflammatory cytckines remains a question. Like assessments of no absorbed disaccharides and antibiotics, studies of possible therapies for hepatic encephalopathy should consider potentially confounding pathogenetic factors and should be carried out in a range of well-defined clinical contexts, if the true value of these interventions is to be evaluated properly.

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