Evolving Concepts: The Negative Effect of Minimal Hepatic Encephalopathy and Role for Prophylaxis in Patients With Cirrhosis

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ABSTRACT

Background: Hepatic encephalopathy (HE), which may be categorized as minimal or overt, is a serious and progressive neuropsychiatric condition that occurs in patients with liver disease or portosystemic shunting. Overt HE (OHE) presents as a wide spectrum of clinical signs and symptoms, ranging in severity from mild confusion to life-threatening coma. Minimal HE (MHE) is a more subtle form of the condition; it is characterized by deficits in cognitive function in patients with a normal clinical examination.

Objective: The purpose was to review the effect of MHE on patients and caregivers, as well as its currently available diagnostic and treatment options.

Methods: A MEDLINE search of published diagnostic assessments, clinical trials, and guidelines from 1985 to 2012 were reviewed and analyzed to assess the potential effect of MHE in the clinical practice setting.

Results: Accumulating evidence suggests that MHE has a substantial negative effect on patient quality of life, particularly in activities that require attention, motor skills, and visuospatial ability. Because MHE lacks obvious clinical signs, specialized testing is required for diagnosis, although there is no consensus on the most appropriate assessment tools or treatment algorithms. Compounds derived from bacterial activities in the gut can cause neurochemical changes in the brain. These gut-derived toxins (eg, ammonia, benzodiazepine-like substances) are implicated in the pathophysiology of OHE. In patients with liver disease or portosystemic shunting, these toxins are inefficiently detoxified, accumulate in the blood, cross the blood-brain barrier, and result in abnormalities such as altered neurotransmission, astrocyte swelling, and impaired energy metabolism. Therefore, treatments have focused on toxin removal and the management of gut flora levels. Several studies have indicated that probiotics, nonabsorbable disaccharides, and nonsystemic antibiotics can all be effective in improving the symptoms of MHE. Furthermore, prophylaxis for MHE in patients with cirrhosis could serve to improve patient quality of life while preventing its transition to OHE.

Conclusions: Although MHE detection and treatment is not currently the standard of care, several therapies have been reported to improve cognitive function and quality of life. Interest is increasing in the proactive diagnosis and management of MHE in the clinical practice setting. However, research is required to determine the conditions under which the putative benefits of prophylactic MHE therapy outweigh the costs. (*Clin Ther*. 2013;35:1458–1473) © 2013 Published by Elsevier HS Journals, Inc.

Key words: cirrhosis, hepatic encephalopathy, minimal, overt, lactulose, probiotics, rifaximin.

INTRODUCTION

Hepatic encephalopathy (HE) is a serious and progressive neuropsychiatric condition that occurs in patients with liver disease or portosystemic shunting.[1–5] It clinically manifests as a spectrum of symptoms encompassing cognitive, intellectual, motor, and psychomotor functions.[6]

Although incompletely defined, the pathogenesis of HE is almost certainly multifactorial. It is likely that an accumulation of gut-derived bacterial toxins, inflammation, and oxidative stress act synergistically to cause cerebral edema and, thus, the symptoms of HE.[7–9] Compounds derived from bacterial activities in the gut can cause neurochemical changes in the

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brain. Increased levels of circulating gut-derived "neuro" toxins (eg, ammonia, benzodiazepine-like substances, short- and medium-chain fatty acids, phenols, mercaptans, and manganese) are implicated in the pathogenesis of HE; indeed, several of the precipitating factors in HE (eg, infection, dehydration, gastrointestinal hemorrhage) involve pathways that affect blood or brain ammonia or toxin levels.[8,10] In patients with liver disease or portosystemic shunting, these toxins are inefficiently detoxified and accumulate in the blood, from where they can cross the blood-brain barrier, resulting in abnormalities such as altered neurotransmission, astrocyte swelling, and impaired energy metabolism.[11,12] Many of the treatments for HE have thus focused on reducing the levels of circulating gut-derived toxins or on the management of gut flora levels, in particular, urease-producing bacteria.[3,13]

HE may be categorized as either minimal (previously identified as subclinical HE) or overt. Overt HE (OHE) presents as a wide spectrum of clinical signs and symptoms that range in severity from mild confusion to life-threatening coma. Minimal HE (MHE) is a more subtle form of the condition, characterized by deficits in cognitive function but with no obvious clinical signs.[14,15] MHE is therefore more difficult to diagnose than OHE, being detectable only by neuropsychometric tests or other specialized assessments. Nevertheless, it is estimated that MHE affects up to 70% of patients with cirrhosis.[16,17]

Extensive research indicates that, despite being relatively asymptomatic, MHE has a substantial negative effect on patients' health-related quality of life (HRQOL) and daily functioning, particularly in activities that require attention, motor skills, or visuospatial abilities (**Table I**).[18–30] Of particular prominence has been the effect MHE has on driving capability; several studies have described its negative effect in this regard under real or simulated driving conditions (**Table I**).[21–27]

MHE is also a risk factor for the more serious OHE, which develops in >50% of patients with MHE within 3 years.[31] Transition to OHE gives rise to poorer outcomes overall, being associated with an overall decline in liver function and short life expectancy[1]; indeed, hospitalized patients with OHE have a 3.9-fold increased risk of death.[32] Furthermore, patients with OHE pose a significant burden to their caregivers, the degree of which is proportional to the severity of cognitive dysfunction.[33] Given all of these facts, together with the effect of MHE on the daily lives of patients, the early detection and management of MHE should be regarded as a priority to prevent its transition to OHE. This review discusses the effect of MHE on patients and caregivers, as well as the currently available diagnostic and treatment options for MHE. A MEDLINE search was conducted for articles published from January 1, 1985, through November 30, 2012, and included the terms covert HE, minimal HE, porto-systemic HE, subclinical HE, lactulose, lactitol, neomycin, nonabsorbable disaccharide, metronidazole, probiotic, rifaximin, and vancomycin. Abstracts of manuscripts not published in English were reviewed if an English-language abstract was available. Abstracts from gastroenterology conferences from 2010 through 2012 were also included in the search. Approximately 100 documents were identified (including primary manuscripts, reviews, and abstracts) for consideration in this review.

DIAGNOSIS OF MHE

Because of the subtle cognitive dysfunction associated with MHE, diagnosis is difficult and requires neuropsychometric and/or neurophysiologic testing.[7,34] However, there is no current consensus about the assessment tools that should be used or on the value of routine testing.[34,35] Neuropsychometric tests, which include pencil-and-paper tests and computerized tests, measure the function of cognitive domains associated with executive functions, vigilance and sustained attention, reaction times and psychomotor speed, and alertness and orientation (**Table II**).[35–49] Of these, the psychometric hepatic encephalopathy score pencil-and-paper test was designed with the specific purpose of diagnosing MHE and was endorsed as a reference standard by the Working Party of the 1998 World Congress of Gastroenterology.[37] However, this test has not been widely used in the United States, likely because of the lack of US-specific normative data and limited availability of the testing system.[36] The Repeatable Battery for the Assessment of Neuropsychological Status™ (Pearson Education, Inc, San Antonio, Texas) has also been suggested as an option for the diagnosis and monitoring of MHE by a commission from the International Society for Hepatic Encephalopathy and Nitrogen Metabolism.[39] Originally designed to serve as a core battery for the assessment of dementia and to track neurocognitive impairment in other disorders,