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Review article

Minimal hepatic encephalopathy: A review

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ABSTRACT

Minimal hepatic encephalopathy (MHE) is the earliest form of hepatic encephalopathy and can affect up to 80% of patients with liver cirrhosis. By definition, MHE is characterized by cognitive function impairment in the domains of attention, vigilance and integrative function, but obvious clinical manifestation are lacking. MHE has been shown to affect daily functioning, quality of life, driving and overall mortality. The diagnosis can be achieved through neuropsychological testing, recently developed computerized psychometric tests, such as the critical flicker frequency and the inhibitory control tests, as well as neurophysiological procedures. Event related potentials can reveal subtle changes in patients with normal neuropsychological performances. Spectral analysis of electroencephalography (EEG) and quantitative analysis of sleep EEG provide early markers of cerebral dysfunction in cirrhotic patients with MHE. Neuroimaging, in particular MRI, also increasingly reveals diffuse abnormalities in intrinsic brain activity and altered organization of functional connectivity networks. Medical treatment for MHE to date has been focused on reducing serum ammonia levels and includes non-absorbable disaccharides, probiotics or rifaximin. Liver transplantation may not reverse the cognitive deficits associated with MHE. We performed here an updated review on epidemiology, burden and quality of life, neuropsychological testing, neuroimaging, neurophysiology and therapy in subjects with MHE.
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1. Introduction

It is well known that 30–45% of patients with cirrhosis develop a spectrum of potentially reversible neurocognitive deficits, termed 'hepatic encephalopathy' (HE) (Poordad, 2007; Stinton and Jayakumar, 2013; Vilstrup et al., 2014). Minimal hepatic encephalopathy (MHE) represents the earliest stage of HE (Dharel and Bajaj, 2015; Morgan et al., 2015).

In fact, the term MHE refers to subtle changes in cognitive function, electrophysiological parameters, cerebral neurochemical/neurotransmitter homeostasis, cerebral blood flow, fluid homeostasis and metabolism, that can be diagnosed in patients with liver disease, with or without portosystemic shunt (PSS), or in patients with PSS without liver disease, and clinical evidence of HE, after the exclusion of overt HE and alternative diagnoses for neuropsychological impairment (Ferenci et al., 2002; Dhiman et al., 2010a,b).

MHE previously known as subclinical or latent hepatic encephalopathy, is by definition, not clinically apparent (Ferenci et al., 2002).

The absent clinical evidence of HE is key to the diagnosis and can only be determined by a detailed anamnestic investigation and a comprehensive neurological assessment of consciousness, cognition, and motor function. Since MHE is often not considered to be clinically relevant, this condition may remain undiagnosed or untreated. However, subjects with MHE perform abnormally on psychometric tests. The neuropsychological disturbances in subjects with MHE mainly involve the executive functions, which include selective attention and psychomotor speed, visuospatial perception, response inhibition and delayed information processing, but other abnormalities may also be observed (Das et al., 2001; Amodio et al., 2004).

The natural history of MHE is worse in patients with poorer liver function; among patients with MHE, the development of overt HE was more common in patients with advanced cirrhosis and a Child–Pugh–Turcotte (CPT) classification score of >6 (Das et al., 2001). The pathogenic mechanism for cognitive impairment in MHE, as well as in overt HE is thought to be extracellular cerebral edema (Donovan et al., 1998; Lin et al., 2012).

In this review we will focus on the studies that have investigated the epidemiology, quality of life, neuropsychological, neuroimaging, neurophysiological abnormalities, as well as therapy, of this important neurological complication of liver diseases.

The MEDLINE, accessed by Pubmed (1966 – March 2015) and EMBASE (1980 – March 2015) electronic databases were searched using the medical subject headings (MeSH) "minimal hepatic encephalopathy", "subclinical hepatic encephalopathy", "liver cirrhosis", as well as the following free terms, combined in multiple search strategies with Boolean operators in order to find relevant articles: "epidemiology", "prevalence", "burden", "quality of life", "neuropsychological tests", "psychometric tests", "neurophysiology", "electroencephalography", "event related potentials", "evoked potentials", "neurophysiology", "neuroimaging", "magnetic resonance imaging", "therapy", "treatment".

Only original or review articles reporting data on studies performed in patients with MHE were considered eligible for inclusion; thus, we excluded articles that were based on patients with HE. The search was limited to studies written in English. Full-text articles were retrieved for the selected titles, and reference lists of the retrieved articles were searched for additional publications. In the case of missing or incomplete data, principal investigators of included trials were contacted and additional information requested. Two review authors screened the titles and abstracts of the initially identified studies to determine if they satisfied the selection criteria. These two reviewers independently assessed the methodological quality of each study and risk of bias, focusing on blinding. Any disagreement was resolved through discussion. The search strategy described above yielded 107 results, 4 of which were excluded after reading the full paper, thereby leaving 103 studies which contributed to this review.

2. Pathophysiology

The pathophysiology of this disease is quite complex, as it involves overproduction of various toxins in the bloodstream and brains (for a review, see Frederick, 2011). Ammonia has been implicated as a key molecule in the pathophysiology of HE, due to its frequent elevation in patients with hepatic cirrhosis and known cellular toxicity, even if the exact mechanisms of ammonia-induced neurologic dysfunction still remain unclear. Glutamine, produced by the metabolism of ammonia, may act as an intracellular osmole and attract water into the astrocytes, thus leading to cerebral edema and probably inducing mitochondrial oxidative dysfunction. Ammonia appears to directly trigger oxidative and nitrosative stress in the astrocyte by increasing intracellular calcium, which also lead to mitochondrial dysfunction and cellular energy failure. Other proposed mechanisms of neuronal dysfunction include ammonia-induced RNA oxidation, activation of mitogen-activated protein kinases and of nuclear factor-κB.

On the other hand, evidence now suggests that ammonia is only a single component in a multifactorial disease process.

In addition to ammonia, many other molecules have been implicated in the pathogenesis of HE. Neurosteroids, such as allopregnanolone, might modulate the gamma-aminobutyric acid (GABA)-A receptors in the brain, enhancing the effects of GABA on these inhibitory receptors.

Endogenous benzodiazepines also activate modulate GABA-A receptors and probably trigger astrocyte swelling via a direct receptor-mediated effect. Indole and oxindole are byproducts of bacterial tryptophan metabolism that have been recently implicated as potential contributors to the pathogenesis of HE. Other putative toxins involved in HE pathogenesis include mercaptans, short-chain fatty acids, false neurotransmitters (e.g., octopamine), manganese, and GABA (Frederick, 2011). Fig. 1 shows an hypothesis of the multifactorial nature of HE.

3. Epidemiology

In 2011 a consensus of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) proposed the introduction of two new terms in HE classification: "covert HE" and "overt HE" (Bajaj et al., 2011a). Overt HE is classified into 3 stages according to severity of consciousness, intellectual function, and behavior impairment. The term covert HE encompasses HE grade 1 and MHE, while according to this classification, patients without HE are considered to be unimpaired (Bajaj et al., 2011a).

The Indian National Association for Study of the Liver (INASL) set up a Working Party on MHE in 2008 with a mandate to develop

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