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EDITORIAL

Minimal hepatic encephalopathy matters in daily life

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Abstract

Minimal hepatic encephalopathy is a neuro-cognitive dysfunction which occurs in an epidemic proportion of cirrhotic patients, estimated as high as 80% of the population tested. It is characterized by a specific, complex cognitive dysfunction which is independent of sleep dysfunction or problems with overall intelligence. Although named "minimal", minimal hepatic encephalopathy (MHE) can have a far-reaching impact on quality of life, ability to function in daily life and progression to overt hepatic encephalopathy. Importantly, MHE has a profound negative impact on the ability to drive a car and may be a significant factor behind motor vehicle accidents. A crucial aspect of the clinical care of MHE patients is their driving history, which is often ignored in routine care and can add a vital dimension to the overall disease assessment. Driving history should be an integral part of care in patients with MHE. The lack of specific signs and symptoms, the preserved communication skills and lack of insight make MHE a difficult condition to diagnose. Diagnostic strategies for MHE abound, but are usually limited by financial, normative or time constraints. Recent studies into the inhibitory control and critical flicker frequency tests are encouraging since these tests can increase the rates of MHE diagnosis without requiring a psychologist. Although testing for MHE and subsequent therapy is not standard of care at this time, it is important to consider this in cirrhotics in order to improve their ability to live their life to the fullest.

Key words: Minimal hepatic encephalopathy; Quality of life; Driving impairment; Diagnosis; Therapy; Prognosis

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INTRODUCTION

Minimal hepatic encephalopathy is a neuro-cognitive dysfunction which occurs in an epidemic proportion of cirrhotic patients, estimated as high as 80% of the population tested. It is characterized by a specific, complex cognitive dysfunction which is independent of sleep dysfunction or problems with overall intelligence[1]. Although named "minimal", minimal hepatic encephalopathy (MHE) can have a far-reaching impact on quality of life, ability to function in daily life and progression to overt hepatic encephalopathy (OHE)[2]. Importantly, MHE has a profound negative impact on the ability to drive a car and may be a significant factor behind motor vehicle accidents. Research in this field is expanding rapidly, but little consensus has emerged regarding standard diagnostic strategies or therapeutic options[3]. The current editorial will focus on the relevance of MHE as an important clinical entity that is ready for evaluation and regular detection not only in research centers but in routine hepatology practice.

PREVALENCE AND IMPORTANCE

With improving management of cirrhotic patients, including those with end-stage liver disease, the neuropsychological care of these patients is being recognized as an unmet need[4-6]. The importance of MHE has been recognized by hepatologists worldwide and of late an explosion of research in this field has occurred[7,8].

Since its first description in the 1970s, MHE has been diagnosed in several countries around the world at a rate of 30%-80%[9,10]. The European experience has shown a high prevalence of MHE in patients who are predominantly non-alcoholic and without any psychoactive drug use[11,12]. The diagnostic methodologies were a combination of neuro-psychometric and neuro-physiologic testing strategies[11-13]. In the United States, the rate of MHE in several research series has been reported to

be 60%-80%, again using a combination of psychometric and neuro-physiologic techniques[14,15].

Experience in Asian countries, especially India, Japan and China, has reconfirmed the high prevalence using locally modified tools[10,16-22]. The diagnostic tools were adapted to the local language and to include illiterate subjects[17,19]. The patient population in these series has included a higher number of patients with viral hepatitis compared to Western series[21,22].

CHARACTERIZATION OF MINIMAL HEPATIC ENCEPHALOPATHY

The importance of MHE lies in its specific deficits. As outlined by Weissenborn *et al*, patients with MHE have defects in attention, vigilance and orientation[23]. These attention deficits in turn lead to learning impairment and difficulties in working memory[12,24]. Psychometric testing in patients with MHE has consistently demonstrated a preservation of overall IQ compared to age-matched controls, indicating that the defects are restricted to certain aspects only[11]. Patients with cirrhosis can also exhibit motor impairments that include Parkinsonian features and features of hepatic myelopathy[25,26]. However, these motor deficits are not included in the typical impairment seen in MHE.

Importantly, deficits in MHE do not extend to the verbal and communication spheres[11]. Similar to OHE patients, there is evidence that patients with MHE have poor insight into their psychometric impairments[27-29]. The preservation of communication skills, lack of symptoms and the poor insight make MHE patients a difficult group to identify with simple questioning in the office.

CONTRIBUTION OF CONCOMITANT DISEASES TO MHE

Patients with specific etiologies of cirrhosis are more likely to exhibit psychometric impairment, specifically chronic hepatitis C. Investigations in the chronic hepatitis C infected groups (both with and without cirrhosis) show a worse psychometric performance compared to patients without chronic hepatitis C in selected studies[30-33]. However, other studies have not demonstrated a difference in psychometric performance of cirrhotics with chronic hepatitis C compared to those without it[30,34]. In addition, a recent detailed study before and after interferon therapy in chronic hepatitis C cirrhotics failed to find an improvement or deterioration during and after therapy completion[35].

Diabetes mellitus is an important correlate of patients with cirrhosis, with the increasing importance of non-alcoholic steatohepatitis, and is also correlated with chronic hepatitis C in the general population[36]. Diabetes mellitus, possibly due to its adverse effect on gastrointestinal motility, has been associated with hepatic encephalopathy[34,37].

Most studies of MHE exclude patients with alcoholic liver disease; therefore, excluding patients with chronic hepatitis C and diabetes mellitus will seriously hinder the generalization of the study. Therefore, a subgroup analysis of chronic hepatitis C and diabetes mellitus within the cirrhosis group or regression adjustment would be necessary for MHE investigation.

CONCOMITANT SLEEP DISTURBANCES

Hepatic encephalopathy is associated with adverse effects on the sleep-wake cycle, especially causing fragmentation of sleep, sleep deprivation and reports of drowsiness during the day[38]. Sleep deprivation *per se* can result in impaired psychometric test performance and as is evidenced in the case of obstructive sleep apnea, and can independently lead to poor driving outcomes[39]. There is debate whether the MHE-associated psychometric impairment is partly due to the inherent sleep-wake cycle disturbances in this condition. Validated sleep and quality of life questionnaire such as Sickness Impact Profile (SIP) sleep scales, Pittsburgh Sleep Quality index and Epworth Sleepiness scale evaluation demonstrate a worse sleep quality and effect on quality of life in patients with MHE[17,38,40]. Steindl *et al* demonstrated a disrupted melatonin cycle in patients with cirrhosis and MHE which was independent of psychometric performance[41]. However, reports have demonstrated that cirrhotics with MHE and sleep disruption do not have worse psychometric performance compared to those who do not have sleep disruption[38,42,43]. This implies that although there is a significant disruption of the sleep-wake and circadian rhythm in patients with MHE, this phenomenon co-exists with the psychometric impairment and is not the cause of it.

QUALITY OF LIFE AND MHE

Quality of life is an essential assessment component of patients with chronic diseases. Issues pertaining to quality of life are also central to most patient complaints in cirrhosis[44]. Groeneweg *et al* studied the Sickness Impact Profile (SIP) in a cohort of cirrhotics being tested for MHE (Medical Outcomes Trust, Boston, MA)[40]. The SIP consists of 136 items which questions patients about 12 sections; sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement (the last three generate a physical sub score), social interaction, alertness behavior, emotional behavior, and communication (comprising the psychosocial sub score). All scales were significantly impaired in MHE patients compared to others. A recent study by Prasad *et al* confirmed these findings in MHE patients in all spheres apart from communication, which was similar between patients with or without MHE[17]. Impaired quality of life has also been demonstrated using the Short Form 36 (SF-36) in MHE populations in several studies across the world[45,46].

Short form-36 (SF-36) is a 36-part questionnaire that has been used in several studies to characterize chronic liver disease and the chronic liver disease questionnaire

has also been used in patients with liver disease[44-47].

The SIP is an extensive survey which requires several minutes to complete, in contrast to the relatively short SF-36. The SF-36, therefore, may be a better tool for clinical practice. However, since quality of life changes in MHE are subtle, the SIP is perhaps the questionnaire better suited for research studies since it can differentiate between small changes in several aspects of QOL.

WORK CAPACITY AND MHE

The specific nature of cognitive dysfunction in MHE results in a disproportionate impairment of workers engaged in "blue-collar" professions compared to "white-collar" professionals. This is essential to remember because cirrhotics engaged in professions that require constant vigilance and coordination, e.g. machinery operators and drivers are affected by MHE more severely compared to those who have predominantly verbal and intellectual functions, such as administrative and company executives[29]. Therefore, MHE not only has the potential to endanger the patients and co-workers during complex occupational tasks, it also can adversely affect their socio-economic status by interfering with work performance[48].

MHE AND PROGRESSION TO OVERT HEPATIC ENCEPHALOPATHY

Overt hepatic encephalopathy portends a poor prognosis and overall survival[49,50]. Patients with MHE have a higher likelihood of development of OHE[14,49,51,52]. Specific subgroups that are more likely to progress to OHE are males, those with a history of OHE, those with alcoholic etiology of cirrhosis and those with varices[19,53,54]. Positive responders to the glutamine tolerance test are also more likely to develop OHE[53]. It is not clear, however, which individual MHE patient will go on to develop OHE. The relative contributions of precipitating factors, such as gastrointestinal bleeding, for OHE development in the context of MHE *versus* no MHE have also not been fully elucidated. Therefore, patients with MHE may be a subgroup requiring close follow-up clinically for OHE development, especially when potential precipitating factors are encountered.

MHE AND DRIVING CAPABILITY

The ability to drive a motor vehicle requires coordination of visual, auditory and vestibular inputs and has the potential to be impaired by metabolic encephalopathies[55].

MHE affects attention, psychomotor function and working memory, all of which are essential for safe driving[56]. Most studies of driving ability using on-road driving tests have demonstrated that MHE patients have significant defects in reaction time, resulting in their pronouncement as unsafe drivers in studies from Germany and Japan[49,57]. Wein *et al* studied the driving ability and rating of driving behavior of 44 patients with cirrhosis using instructors masked to their status. Fourteen of these patients had been diagnosed with MHE[58]. Results showed that patients with MHE required interventions by the driving instructor to prevent an accident at a rate 10 times higher compared to those with MHE and controls. Specific driving behaviors were also rated worse in patients with MHE, especially car handling, adaptation, cautiousness and maneuvering[58].

Another essential skill required for safe driving is navigation, which ensures that the subject is in the right place at the right time[55]. Given the working memory abnormalities in cirrhotic patients, the study of navigation in MHE is important[24]. Our group recently published a study evaluating the performance of cirrhotics to age and education-matched controls on a driving simulator. Navigation skills in MHE are adversely affected[59]. All patients underwent a driving simulation which also included a navigation task. This task consisted of driving through a "virtual city" and illegal turns off the marked path were recorded. There was a significantly higher rate of illegal turns in the MHE group compared to those without MHE and controls. Illegal turns were proportionate to impairment in psychometric performance in cirrhotic group[59]. Therefore, driving difficulties in patients with MHE are likely multi-dimensional and includes impairment in reaction time and navigation skills.

DRIVING OUTCOMES IN PATIENTS WITH CIRRHOSIS AND MHE

Traffic accidents are one the leading causes of death worldwide, especially in young adults, the most productive age group of any society. It is important to determine whether patients with MHE also have poor driving outcomes compared to those without MHE and controls. This would be essential in formulating public health decisions regarding licensing and therapy for MHE. A study published by our group sent an anonymous driving outcome questionnaire to controls, cirrhotics tested for MHE and cirrhotics not tested for MHE due to concurrent psychoactive drug use[60]. As many as 33% of MHE patients reported having a traffic accident or violation within the last year compared to only 4% of MHE negative patients and 12% of the patients using psychoactive drugs. When 5 year data were analyzed a significant majority of MHE patients (53%) reported a traffic accident or violation compared to only 23% of MHE negative patients and 22% of those on psychoactive drugs. This is even more significant since none of the MHE patients were drinking alcohol. On multi-variate analysis, MHE emerged as the sole factor associated with traffic violations [odds ratio 6.0 (CI 1.2-31.3)], motor vehicle accidents [odds ratio 7.3 (CI 2.1-33.2)] and both [odds ratio 7.6 (CI 1.5-37.3)][60]. However, despite these striking numbers, there is still the need to analyze driving data prospectively using identified records before making specific recommendations regarding driving capability[3].

Patients with cirrhosis have a poor prognosis after trauma and surgery, especially with increasing Child-

Pugh score[61]. A combination of coagulation impairment, sepsis and hepatic dysfunction has been noted as contributing factors to this worse prognosis[61]. A study of a large inpatient sample from the United States showed that patients with cirrhosis who were involved in a motor vehicle crash had a higher mortality than those who were admitted for motor vehicle crashes only[62]. Despite a younger average age, patients with cirrhosis and crash had a similar mortality compared to those admitted with cirrhosis only. Hospitalization charges and inpatient stay were also significantly higher in cirrhotics with crash compared to patients admitted for cirrhosis only and those admitted for motor vehicle accidents only. On multi-variate regression within the patients admitted with motor vehicle accidents, age > 65 years and cirrhosis were the variables most significantly associated with mortality[62].

Therefore, not only are patients with MHE more likely to get into an accident, they are also more likely to die from it and utilize greater resources as a result of the accident. All these factors make it essential for a clinician to take a driving history when evaluating patients for cirrhosis and chronic liver disease.

MHE: INSIGHT INTO THE DISEASE PROCESS AND DRIVING SKILLS

Insight into personal deficits is essential in patients in order to seek medical intervention. Anosognosia, defined as the unawareness of a disease, is a key component of the disease process in several metabolic and vascular cerebral disorders[63,64]. This phenomenon is clearly observed in patients with OHE, in which it is the persons in the environment who detect changes in the patients' sensorium rather than the patient[27]. A recent report extended this lack of insight into driving impairment. This study demonstrated that patients with MHE rated themselves as significantly better drivers compared to those without MHE and controls when they were evaluated by independent observers[28]. Therefore, similar to patients with OHE, it may be important to elicit a complete driving history and assessment from relatives familiar with the MHE patients' driving rather than relying on the patients' history alone.

THE HISTORY NOT TAKEN: DRIVING HISTORY

The standard of care of patients with cirrhosis without any ongoing acute issues is focused on strategies aimed to prevent decompensation. These strategies are aimed at reducing mortality and morbidity from a liver disease standpoint. However, as evidenced by recent reports, patients with cirrhosis and MHE also are at risk for developing morbidity and mortality behind the steering wheel[58,60]. An objective driving history, including confirmation from the local supervisory agency, and corroboration of driving skills by relatives is also an essential aspect of patient care. The driving history to the clinical history would arguably be a vital addition to the overall understanding of the disease severity from a clinical and psychosocial view in cirrhosis.

TESTING FOR MHE DURING CLINIC VISITS

Although the majority of surveyed hepatologists in Spain and the United States agreed that MHE was a significant problem requiring testing, the minority were able to actually test for MHE as part of their clinical practice[7,8]. Main barriers to MHE testing were inability to get tests paid for by insurance, adding time to clinic visits and lack of standardized norms for the United States[8].

The psychometric battery recommended by the Working Group on Hepatic Encephalopathy is the PSE-syndrome test published by Weissenborn *et al*[2,11]. This test battery, although quite efficient in diagnosing MHE, requires a psychologist and valid population norms. The difficulty of applying these tests in the United States is the lack of background population norms and the need for a licensed psychologist to order and administer these tests. In addition, these are still not routinely covered by private health care insurance. These logistic barriers have effectively prevented routine clinic diagnosis of MHE.

The AASLD survey also highlighted the need for simpler and rapid testing that can take the place of cumbersome and copyrighted psychometric testing[8]. The inhibitory control and the critical flicker frequency have emerged as tests that can be applied in clinical practice without the need for psychological expertise[3,13,14,20,65]. However, detailed validation studies are still underway for these tests.

POPULATION TO BE TESTED

Patients with cirrhosis who are ambulatory and capable of independent living are the ones most affected by MHE and should definitely be tested. Previous recommendations have been split regarding the specific population to be targeted for testing. Ortiz *et al* and Stewart *et al* have specifically recommended certain patient populations be tested[1,48]. Psychometric performance can be affected by current alcohol use, use of psychoactive drugs and pre-existing neurological disorders[11]. In cirrhotics who do not fulfill these criteria, it is in the best interest of the patient to be offered testing at the initial visit regardless of their subsequent activities. There is no consensus regarding the frequency of testing, but experience has shown relative similarity in psychometric scores at 6 mo intervals in the absence of acute clinical and neurological events such as development of OHE[19].

THERAPY FOR MHE

Treatment of MHE improves psychometric performance and quality of life[16,17].

A recent consensus conference promulgated lactulose as the first choice of therapy for MHE in concor-

dance with the previous study data and the AASLD survey[3,8]. However, whether this would have any effect on development of OHE, driving capability or overall survival remains to be investigated. Since driving and psychometric impairments are highly correlated, it is reasonable to expect that driving performance would also improve after MHE therapy.

However, the adherence rate of lactulose in patients with OHE is low; therefore, to expect an MHE patient, who does not have any specific symptoms and lacks insight into their problems, to be adherent on a medication that could cause diarrhea and flatulence is difficult[3,66]. Therefore, alternatives to lactulose have also been studied for MHE. Liu *et al* showed that fiber and fiber with probiotics improved psychometric function and importantly the Child class of patients[21]. Similar studies have been published using various formulations of probiotics with good improvement in psychometric tests[67-71]. Our group has recently completed a randomized control trial of a probiotic yogurt that resulted in a significant reversal of MHE in the yogurt-randomized group compared to the group randomized to no treatment[72]. The adherence was excellent and none of the yogurt-treated group developed OHE. Although probiotics are attractive options that spare the patients from the poor palatability of lactulose, difficulties in the availability and the standardization of probiotic organisms remain. However, these preliminary data suggests that dietary intervention may be considered in addition to probiotics for amelioration of MHE.

Therefore, although treatment options for MHE are evolving, it is still important to test patients to offer them the available therapeutic options.

CONCLUSION

MHE is an epidemic cognitive dysfunction in patients with cirrhosis which is gaining importance in clinical and research spheres due to improved survival in cirrhotic patients.

MHE patients exhibit a specific cognitive impairment that negatively impacts their driving capability and work performance and importantly is not evident to the patients themselves.

A crucial aspect of the clinical care of MHE patients is their driving history, which is often ignored in routine care and can add a vital dimension to the overall disease assessment. Driving history should be an integral part of care in patients with MHE.

The lack of specific signs and symptoms, the preserved communication skills and lack of insight make MHE a difficult condition to diagnose.

Diagnostic strategies for MHE abound, but are usually limited by financial, normative or time constraints. Recent studies into the inhibitory control and critical flicker frequency tests are encouraging since these tests can increase the rates of MHE diagnosis without requiring a psychologist.

Although testing for MHE and subsequent therapy is not standard of care at this time, it is important to consider this in cirrhotics in order to improve their ability to live their life to the fullest.

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