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## Detection of Minimal Hepatic Encephalopathy in Iranian Patients with Cirrhosis

Mahsa Khodadoostan<sup>1</sup>, Sina Sadeghian<sup>2,\*</sup>, Ali Safaei<sup>2</sup>, Milad Kabiri<sup>3</sup>, Sara Shavakhi<sup>4</sup>, Ali Reza Shavakhi<sup>4</sup>, Ahmad Shavakhi<sup>5</sup>

1. Assistant Professor of Gastroenterology and Hepatology, Department of Gastroenterology and Hepatology, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
2. Student of Medical Sciences, Department of Gastroenterology and Hepatology, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
3. Student of Medical Sciences, Department of Gastroenterology and Hepatology, Mazandaran University of Medical Sciences, Mazandaran, Iran
4. Student of Medical Sciences, Department of Gastroenterology and Hepatology, Shahr-e-kord University of Medical Sciences, Shahr-e-kord, Iran
5. Professor of Gastroenterology and Hepatology, Department of Gastroenterology and Hepatology, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

### \* Corresponding Author:

Sina Sadeghian, MD  
Department of Gastroenterology and Hepatology, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran  
Telefax: + 98 31 36412358  
Email: sadeghian.sina72@gmail.com

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### ABSTRACT

#### BACKGROUND

Minimal hepatic encephalopathy (MHE) is the mildest type of hepatic encephalopathy in patients with cirrhosis. Patients with MHE have normal clinical and physical examination but they show some neurocognitive dysfunctions that affect their quality of life negatively. The aim of the current study is to diagnose MHE in patients with cirrhosis and its associated factors.

#### METHODS

This is a cross-sectional study on 120 known cases of cirrhosis referred to hospitals affiliated to Isfahan University of Medical Sciences during 2014-17. The patients' cirrhosis severity was evaluated using laboratory tests and physical examinations based on MELD (Model for End-stage Liver Disease) and Child-Pugh criteria. The patients' demographics were filled in a checklist. All included patients with cirrhosis were asked to respond to the questions of Psychometric Hepatic Encephalopathy Score (PHES) test.

#### RESULTS

Mean age of the patients was  $51.2 \pm 9.7$  years. 62 (51.7%) patients were men and 58 (48.3%) patients were women. The mean score of the patients based on MELD criteria was  $14.03 \pm 6.09$ . 26.7% of the patients presented MHE. Mean age of the patients with MHE was statistically less than the patients without MHE ( $p$  value  $< 0.001$ ). Mean score of MELD criteria among the patients with diagnosis of MHE was significantly higher than the other group ( $p$  value  $< 0.001$ ). The patients' Child class was statistically associated with MHE ( $p$  value  $< 0.001$ ). Men were significantly more affected than women ( $p$  value = 0.03).

#### CONCLUSION

MHE was associated with MELD score and Child class of the patients with cirrhosis. The noticeable point was reversible association of age with MHE. Further studies are recommended.

#### KEYWORDS:

Cirrhosis, Minimal hepatic encephalopathy, MELD score, Child-Pugh class

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### INTRODUCTION

Hepatic encephalopathy (HE) is a common serious complication of cirrhosis, which is associated with spectrum of neuropsychological dysfunctions. HE can significantly cause morbidity and mortality in such patients.<sup>1</sup>

Various etiologies have been provided for HE, of them the most common one is the theory of endogen neurotoxic metabolites of ammonia produced by the body. These products should be metabolized in the liver while patients with cirrhosis have lost this ability.<sup>2</sup>



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**Table 1: Hepatic encephalopathy grading**

Hepatic encephalopathy type	Manifestations
I	Changes in behavior, mild confusion, slurred speech, disordered sleep
II	Lethargy, moderate confusion
III	Marked confusion (stupor), incoherent speech, sleeping but arousable
IV	Coma, unresponsive to pain

HE is a condition that based on signs and symptoms has been divided to four subgroups (table 1).<sup>3</sup> HE may have some complications including pneumonia aspiration, cortical blindness, brain edema, and neurological deficits. The mildest form of HE is known as minimal hepatic encephalopathy (MHE).<sup>2</sup> Patients with MHE have normal clinical and physical examination of mental status but such patients show some cognitive dysfunctions that can only be diagnosed through neuropsychological and neurophysiological tests.<sup>2,4</sup> Patients with MHE may improve, remain unchanged, or deteriorate and develop overt HE over a long-term follow-up. The areas with impairments in patients with MHE are attention, visuospatial perception, speed of information processing, especially in the psychomotor area, fine motor skills, and short-term memory.<sup>5,6</sup>

MHE shows mild cognitive function changes of electrophysiological parameters, neurotransmitter homeostasis, brain blood flow, and brain metabolism. Although these changes are not easily recognizable in cirrhotic patients with MHE<sup>7</sup> but it can affect health related quality of life in these patients negatively. These effects include information processing speed reduction, personality disorders, sleep disorders, and motor dysfunction. One of the considerable points in such patients is their relative inability in performing personal tasks such as driving.<sup>8,9</sup>

The prevalence of MHE has been from 30% to 84% in patients with cirrhosis. These differences may be due to different means of measurements and also variety of societies.<sup>4,10</sup>

There is no evidence showing that the prevalence of MHE among Iranian patients with cirrhosis has been assessed previously. In addition, studies of other communities in this term, are limited and with small study population. Considering the importance of MHE diagnosis and few numbers of studies about this issue, we have decided to conduct the current study to find MHE in patients with cirrhosis.

## MATERIALS AND METHODS

This is a cross-sectional study on 120 known cases of cirrhosis referred to Al-Zahra Hospital, a referral center for gastrointestinal diseases affiliated to Isfahan University of Medical Sciences during 2014-17.

Patients with the minimum age of 18 years and diagnosis of cirrhosis based on laboratory tests, radiological images, and/or biopsy sampling were included. Those with overt encephalopathy, known intracranial lesions, active gastrointestinal bleeding, progressive active infection, renal function impairment (serum creatinine > 2 mg/dL), electrolyte disturbances (serum sodium < 130 or > 150 meq/dL and/or serum potassium < 3.0 or > 5.5 meq/dL) and patients who were receiving treatment for HE such as lactulose or antibiotic for the previous 8 weeks or with the history of benzodiazepines, narcotics, opioids and/or alcohol use in this duration were excluded from the study. In addition, patients who were not able to answer the questions for any reason were excluded as well. Also, all patients with signs and symptoms of moderate or severe HE including asterixis, confusion, lethargy, seizure, and personality and thinking changes in their history and physical examination were excluded from the study.

The method of sampling was non-randomized consecutive. In this order, all patients who were referred to Al-Zahra Hospital were assessed until the study population was completed.

The severity of the patients' cirrhosis was evaluated using laboratory tests and physical examinations based on MELD (Model for End-stage Liver Disease) and Child-Pugh criteria.<sup>11</sup>

All included patients were interviewed by a single gastrointestinal specialist and were asked to respond to the questions of Psychometric Hepatic Encephalopathy Score (PHES) test.<sup>2,12</sup> PHES includes number connection tests A and B, the digit symbol test, the line tracing test, and the circle dotting test.<sup>5</sup>

The score was measured for each patient according to their age and level of education (PHES RedeH).<sup>13</sup> In case of score < 4 or complete inability to perform two numbers of the above tests, the patient was diagnosed as having MHE.

The data were analyzed using IBM SPSS software version 20. Descriptive data were reported in mean ± standard deviation. For analytic data, Chi-square and ANOVA tests were used. *P* values less than 0.05 were considered as statistically significant.

**Table 2: Distribution of etiology, Child-Pugh class, and presence of minimal hepatic encephalopathy in patients**

Variables		N	%
Etiology	Viral	51	42.5
	Non-alcoholic hepatic failure	19	15.8
	Alcoholic hepatic failure	20	16.7
	Not known	9	7.5
	Others	21	17.5
Child-Pugh class	A	78	65
	B	37	30.8
	C	5	4.2
Presence of minimal hepatic encephalopathy	Yes	32	26.7
	No	88	73.3

**Table 3: Mean age and cirrhosis severity based on MELD considering MHE status (Model for End-stage Liver Disease; Minimal hepatic encephalopathy)**

Variable	MHE positive (mean ± SD)	MHE negative (mean ± SD)	P value
Age	44.3 ± 9.1	53.8 ± 8.7	< 0.00
MELD score	21.8 ± 5.8	11.2 ± 2.8	< 0.001

**Table 4: MHE distribution based on Child-Pugh class, sex, and etiology (MHE: Minimal hepatic encephalopathy)**

Variables		MHE (number (%))	P value
Child-Pugh class	A	3 (3.8%)	< 0.001
	B	24 (64.9%)	
	C	5 (100%)	
Sex	Female	11 (19%)	0.03
	Male	21 (33.9%)	
Etiology	Viral	13 (25.5%)	0.74
	Non-alcoholic hepatic failure	4 (21%)	
	Alcoholic hepatic failure	6 (30%)	
	Not known	4 (44.4%)	
	Others	5 (23.8%)	

## RESULTS

In the current study, 120 patients with cirrhosis with the mean age of  $51.2 \pm 9.7$  years (range: 27-75 years) were evaluated. 62 patients (51.7%) were men and 58 (48.3%) were women.

The mean MELD score of the patients was  $14.03 \pm 6.09$ . Information about cirrhosis status of the patients based on Child-Pugh criteria and presence of MHE is demonstrated in table 2.

MHE was diagnosed in 32 patients (26.7%). Mean age of the patients affected with MHE was less than cirrhotic patients without MHE ( $P < 0.001$ ). Mean score of MELD criteria among the patients with diagnosis of MHE was significantly higher than the other group ( $P < 0.001$ ) (table 3).

Rate of MHE was significantly higher among men ( $P = 0.03$ ) but it was not in association with the etiology of cirrhosis ( $P = 0.74$ ).

There was a significant association between Child-Pugh class and MHE. In this term, the patients with class C cirrhosis were affected more than the patients class B and those with class B were affected more than the patients with class A (table 4).

## DISCUSSION

MHE is a crucial reversible condition that affects patients' quality of life and daily activity steeply and negatively. Several studies have recommended MHE therapy due to its improvement (Several studies have insisted on

reversibility of hepatic encephalopathy in its minimal phase; thus therapeutic considerations for prevention and treatment of this condition is recommended). In fact treatment of MHE can delay its progression and also improve the quality of life thus promotes life expectancy. On the other hand, based on time-consuming neuropsychological tests, hepatologists rarely spend time to screen patients with MHE.<sup>14-16</sup> What has been mentioned above shows the importance of diagnosing MHE in patients with cirrhosis.

Different studies have presented various prevalence of MHE among patients with cirrhosis. These differences may have occurred based on the type of neurophysiological and neuropsychological screening tests that they have used for their patients. Generally, the prevalence of MHE has been estimated from 20% to 80% in various studies.<sup>4,17</sup> In the current study we detected MHE in 26.7% of our patients while Praveen Sharma and colleagues in another study conducted in the Middle East reported MHE in 41% of their assessed patients.<sup>18</sup>

We found that MELD score was significantly associated with the incidence of MHE. In addition, Child class as a manifestation of hepatic failure severity and also a predictor of surveillance of patients with cirrhosis has been found in accordance with the presence of MHE. In fact, we found that 100% of the patients with Child class C presented HE while 64.9% of the patients with Child class B and 3.8% of the patients with Child class A presented MHE. These results are comparable with other studies as previous reports have presented controversial results. For instance, in a study by Praveen Sharma and others MHE was significantly associated with MELD score and MELD score > 15.5 was in accordance with the incidence of MHE. Similarly, Meyer and co-workers found that the higher MELD score the more trail-making test A and B impaired.<sup>19</sup> This result is in contrast to the study of Yoo and colleagues who found no association between the patients' MELD score and neurophysiological study using electroencephalogram.<sup>20</sup> The next point is assessment of Child class with the neurocognitive function of patients with cirrhosis. Chen and co-workers in their study presented that Child score was independently associated with MHE and also patients' surveillance.<sup>21</sup>

Age and sex distribution of MHE among patients with cirrhosis was the next assessment of our study. Although sex distribution of the studied patients was not notably

different but MHE occurrence was significantly higher among men. This sex distribution may show the severity of cirrhosis, which may be worse among men as we have not compared Child class between men and women. It should be mentioned that there are studies that have presented results similar to ours such as the studies by Chen and Goyal and their co-workers that reported male involvement in over 70% of their patients.<sup>21,22</sup>

Another considerable point about our patients is the age of the patients at the time of MHE detection. In the current study the patients with MHE were significantly younger than those without hepatic encephalopathy. It can be hypothesized that younger patients were more sensitive to level of ammonia in comparison with elder patients. Also other hypothesis can be considered such as earlier onset in younger cases, or maybe higher Child-Pugh score of younger patients, which we have not assessed in the current study. Further studies are recommended. Chen and colleagues presented diverse results as they found no association between MHE affected patients' age and not-affected ones.<sup>21</sup> Yu-Yuan Li and co-workers found higher rate of MHE in their older patients but they have presented that MHE occurrence was in relation with the patients' level of education as well.<sup>23</sup> The results of the study by Mina and colleagues were somewhat different as they found MHE in their older patients but not significantly.<sup>4</sup>

## CONCLUSION

Based on our findings, MHE was associated with the MELD score and Child class of the patients with cirrhosis. In addition men were more affected by MHE. The noticeable point about our patients was the association between age and the incidence of MHE as we found a reverse association between the patients' age and MHE incidence. Further studies in this matter are recommended.

### Limitations:

In the current study we have not assessed patients' age at the onset of cirrhosis, duration of cirrhosis, and the level of ammonia.

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## ETHICAL APPROVAL

There is nothing to be declared.

## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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