ANNALS of Hepatology

Vol. 10 Suppl.2, 2011: S40-S44

Prevalence of minimal hepatic encephalopathy in cirrhotic patients

Héctor Jesús Maldonado-Garza,* Genaro Vázquez-Elizondo,* Juan Obed Gaytán-Torres,* Ángel Ricardo Flores-Rendón,* Martha Graciela Cárdenas-Sandoval,* Francisco Javier Bosques-Padilla*

* Centro Regional para el Estudio de las Enfermedades Digestivas, Hospital Universitario "José E. González". Monterrey, Nuevo León, México.

ABSTRACT

Background. Minimal hepatic encephalopathy (MHE) has implications for health-related quality of life as well as for survival of cirrhotic patients, but a standardized diagnostic test is not available. **Objective.** To determine the prevalence of MHE among cirrhotic patients by using the psychometric hepatic encephalopathy score (PHES) system and the critical flicker frequency (CFF) test to diagnose MHE and to identify factors that influence the results of these tests. **Material and methods.** From April 2007 to March 2008, PHES and CFF tests were performed on patients with cirrhosis but no overt hepatic encephalopathy. Descriptive statistics were used to express the results and the Spearman correlation was used to evaluate CFF and PHES results according to age and education level. **Results.** We studied 104 patients. The prevalence of MHE was 55.8% (n = 58) based on a positive result for either the PHES or the CFF test, 32.7% (n = 34) based on positive PHES results alone, 34.6% (n = 36) based on positive CFF test results alone and 11.5% (n = 12) based on a positive result for both tests. According to PHES, the incidence of MHE was correlated with education level (r = 0.333, p = 0.001), but not with age. According to CFF, the incidence of MHE was correlated with age (r = -0.93, p = 0.049), but not with education level. **Conclusion.** The prevalence of MHE was similar to that previously reported. Patient literacy influences MHE diagnosis with PHES but not with CFF. CFF is a simple and feasible method that identifies patients with MHE who may benefit from treatment independently of their education level.

Key words. Minimal hepatic encephalopathy. Critical flicker frequency. Psychometric hepatic encephalopathy score. Survival. Educational level.

INTRODUCTION

Liver disease constitutes one of the main causes of mortality worldwide.[1] In Mexico, chronic liver disease was the second highest cause of mortality from 2000 to 2008 among the economically active population (15-64 years old), with an estimated incidence of 25.5 to 28.9 cases per 100,000 inhabitants.[2] Hepatic encephalopathy (HE) constitutes one of the principal markers of survival among patients with cirrhosis. As hepatic reserve declines, the probability of acute HE episodes increases, thus reducing survival.[3-4] Although it is part of the spectrum of HE, minimal hepatic encephalopathy (MHE) does not manifest clinically, as there are no overt signs or symptoms. The prevalence of MHE has been estimated to be between 20 and 74%, but a gold standard for diagnosis has not yet been developed.[5-9]

Diagnosing MHE is of great importance because of its effect on quality of life, that is, on the patient's ability to tolerate adverse daily events,[10-11] and its presence confers a higher overt HE.[6-7] However, few experimental studies[12-13] or clinical trials[14-15] have been conducted to characterize the association between MHE and HE. A recent publication by the American Association for the Study of Liver Diseases recommends that MHE should be diagnosed and treated.[16] Evidence from neurocognitive studies has concluded that MHE primarily affects areas related to the attention and visuospatial domains.[17] Therefore, tests that assess the status of these domains should have good diagnostic reliability. In particular, the psychometric hepatic encephalopathy score (PHES) has proven to be useful for MHE diagnosis.[18] In addition, the critical flicker frequency

Correspondence and reprint request: Francisco Javier Bosques Padilla, M.D.
Hospital Universitario de Monterrey Dr. José Eleuterio González
Universidad Autónoma de Nuevo León. Madero y Gonzalitos s/n.
Col. Mitras Centro. Monterrey, N.L., México
Tel.: (52) (81) 8333-3664. Fax: (52) (81) 8348-6068
E-mail: fbosques58@hotmail.com

Manuscript received: May 05, 2010.
Manuscript accepted: May 06, 2010.

(CFF) test has been demonstrated to be a useful, reliable and easy-to-perform test for diagnosing MHE.[19-21] CFF results have a strong correlation with PHES results,[22] and do not require standardization for age or literacy, both of which are required for PHES assessment.[23] We conducted this study because information on the prevalence of MHE among the Mexican population, which is currently lacking, would enable the quality of life of this group to be improved. We evaluated the PHES and the CFF test in terms of diagnostic accuracy for MHE and determined whether age or education level influences the results of these tests.

MATERIAL AND METHODS

Patient selection

From April 1, 2007, to March 31, 2008, we enrolled patients with a diagnosis of compensated cirrhosis that was confirmed by clinical or biochemical methods, radiological studies or a liver biopsy. We excluded patients with evident HE according to the West Haven Criteria[24] or a history of previous decompensated liver disease (variceal bleeding, hepatorenal syndrome, hepatocellular carcinoma), as well as those who used psychoactive drugs (psychotropic, antiepileptic or illegal drugs, or alcohol). No patients were excluded because of portosystemic shunts.

A diagnosis of alcohol-related liver disease was made when daily alcohol consumption was > 80 g for men or > 30 g for women and the patients were negative for viral, metabolic and autoimmune markers.[25] Diagnosis of hepatitis C or B virus-related liver disease was conducted using specific viral serology (HBsAg or anti-HCV). Autoimmune liver disease was diagnosed using specific autoimmune markers (antinuclear antibodies, anti-smooth muscle antibodies or liver-kidney antimicrosomal antibodies).[26] Nonalcoholic liver disease was defined as the presence of metabolic syndrome in the absence of significant alcohol consumption (< 140 g/week) or was identified using histological methods.[27] Patients whose diagnostic workup did not identify an etiology were classified as having cryptogenic cirrhosis.[28] Education level was classified according to academic grades currently used by the public education system in Mexico.[29]

Neuropsychiatric evaluation

- ***Psychometric hepatic encephalopathy score.*** The PHES battery was applied using the Spanish standardization, and results were corrected according to the normality tables for age and education level (available from: http://www.redEH.org) and were expressed in points. PHES was considered abnormal when the score was two standard deviations greater than the mean of the paired controls (score < 4).[18]
- ***Critical flicker frequency.*** To measure CFF, we used a portable Hepatonorm Analyzer® (R&R Medi-Business Freiburg GmbH, Freiburg, Germany).[19,21-22] Measurements were conducted between 13:00 h and 16:00 h in a quiet, isolated and weakly illuminated room. CFF was considered abnormal when the value was < 38 Hz.

Statistical analysis

Data were expressed as frequencies and percentages according to the presence or absence of MHE. Continuous variables were expressed as the mean ± standard deviation. The relationships between PHES and CFF and age and education level were evaluated using Spearman's rank correlation coefficient. Statistical analysis was performed using SPSS software for Windows, version 17.0 (SPSS, Chicago, IL).

Ethical considerations

Every patient included in the study signed an informed consent form to undergo CFF and PHES testing. The study was approved by the Ethics Committee of the Hospital Universitario de Monterrey according to the Helsinki Declaration (1989) for human research.

RESULTS

We enrolled 104 patients who fulfilled the inclusion criteria. Complete follow-up for 2 years was achieved for all patients except those who died. Patient demographic and clinical characteristics are shown in table 1.

MHE prevalence

The prevalence of MHE was 54.8% (n = 57) based on a positive result for either the PHES or the CFF test, 31.7% (n = 33) based on positive PHES results alone, 34.6% (n = 36) based on positive CFF test results alone and 11.5% (n = 12) based on a positive result for both tests. The prevalence of MHE according to Child-Pugh status is shown in figure 1. Note

Table 1. Demographic and clinical characteristics of patients enrolled in this study.

Variable	Total (n = 104)	Patients with MHE (n = 57)	Patients without MHE (n = 47)
• Age (mean ± SD)	49.6 ± 11.1	51.1 ± 11.2	47.9 ± 10.6
• Sex			
Male	75 (72)	37 (64.9)	38 (81)
Female	29 (28)	20 (35)	9 (19)
• Cirrhosis etiology			
Alcohol	72 (69.2)	38 (66.7)	34 (72.3)
Viral	7 (6.7)	4 (7)	3 (6.4)
Autoimmune	6 (5.8)	3 (5.2)	3 (6.5)
Other[§]	19 (18.3)	12 (21.1)	7 (14.9)
• Education level			
Illiterate	0	-	-
Incomplete elementary school	27 (26)	20 (35.1)	6 (12.8)
Elementary school completed	30 (28.8)	17 (29.8)	14 (29.8)
Secondary school	29 (27.9)	11 (19.3)	18 (38.3)
Middle-Senior high school	14 (13.5)	9 (15.8)	5 (10.6)
College	4 (3.8)	0	4 (8.5)
• Child-Pugh status			
A	46 (44)	20 (35.1)	26 (55.3)
B	29 (28)	17 (29.8)	12 (25.5)
C	29 (28)	20 (35.1)	9 (19.1)
• Diuretic use	29 (27.8)	21 (40.4)	8 (19.5)
• Beta-blocker use	78 (75)	42 (73.6)	36 (76.7)

[§]Nonalcoholic steatohepatitis (n = 2), cryptogenic cirrhosis (n = 16), metastatic liver disease (n = 1). SD: Standard deviation. MHE: Minimal hepatic encephalopathy.

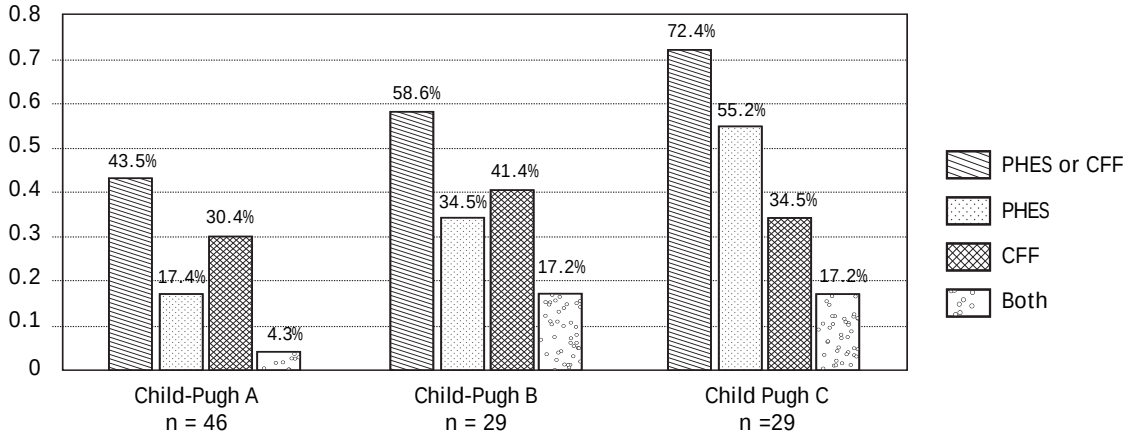

Figure 1. *MHE prevalence according to Child-Pugh status and diagnostic method.*

that the prevalence of MHE among Child-Pugh class C patients was 72.4% (n = 21).

Correlation of PHES and CFF with age and education level

Spearman correlation analysis showed that PHES was correlated with education level (r = 0.333, p = 0.001) but not age (Table 2). Conversely, CFF was correlated with age (r = -0.93, p = 0.049) but not education level (Table 2 last column).

DISCUSSION

The prevalence of MHE among our population of cirrhotic patients according to a positive PHES or CFF test result was 54.8%, which is among the highest prevalence rates reported in

Table 2. Correlations between age, education level, CFF and PHES.

Variable	Digit symbol test	Number connection test A	Number connection test B	Serial dotting test	Line tracing test	Total	CFF
Age	r = –0.526 p < 0.001	r = 0.424 p < 0.001	r = 0.444 p < 0.001	r = 0.326 p < 0.001	NS No correlation	NS No correlation	r = -0.93
Education level	**r = 0.621** **p < 0.001**	**r = -0.603** **p < 0.001**	**r = -0.593** **p < 0.001**	**r = -0.408** **p < 0.001**	**r = -0.292** **p = 0.003**	**r = 0.333** **p = 0.001**	NS No correlation
CFF	r = 0.195 p = 0.047	r = -0.349 p < 0.001	NS No correlation	NS No correlation	NS No correlation	NS No correlation	

PHES: Psychometric hepatic encephalopathy score. CFF: Critical Flicker Frequency Test.

the literature.[6-7,9,11,30] MHE is associated with subjacent liver reserve, as demonstrated by a high frequency among Child-Pugh class C patients (72.4%, n = 21) (Figure 1), as has been reported previously.[6,31] The most common etiology was excessive alcohol consumption, which concurs with the epidemiology of chronic liver disease in Mexico.[32]

For MHE diagnosis, neurofunctional tests for cirrhotic patients should ideally assess various aspects of cerebral function. In this study, we employed the PHES battery, which assesses the abstract and psychomotor domains and can identify subtle alterations in neuronal coordination of the encephalon[18,23] as well as extrapyramidal alterations.[33] The CFF test enables assessment of alterations in the visuospatial domain via stimulation of retinal neurons (Müller glial cells),[34] the conduction of which is affected by low-grade edema and thus MHE. Data from PHES assessments are usually standardized according to age and literacy. Our results demonstrate that education level affects the diagnostic accuracy of PHES for MHE, even though the Spanish reference tables were used.[18,23] This phenomenon was not observed for CFF, but its diagnostic accuracy was affected by age. Further study of the effect of age on the diagnostic accuracy of CFF for MHE is warranted.

CONCLUSION

The prevalence of MHE was high in our study population. MHE can be diagnosed using either the PHES or CFF test, but the diagnostic accuracy of PHES may be affected by literacy. Although age affected the diagnostic accuracy of CFF, this effect may be associated with neuronal degeneration and should be confirmed by larger controlled trials. Nonetheless, CFF remains a useful method in the diagnostic workup for MHE.

REFERENCES

1. Bosetti C, Levi F, Lucchini F, Zatonski WA, Negri E, La Vecchia C. Worldwide mortality from cirrhosis: an update to 2002. *J Hepatol* 2007; 46: 827-39.
2. Principales causas de mortalidad en edad productiva (de 15 a 64 años), periodo 2000 a 2008. Secretaría de Salud, 2008 (Accessed Julio 1 2010). Available from: www.sinais.salud.gob.mx/descargas/xls/m_009.xls.
3. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; 44: 217-31.
4. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transpl* 2007; 13: 1366-71.
5. Poordad FF. Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* 2007; 25(Suppl. 1): 3-9.
6. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J Gastroenterol Hepatol* 2001; 16: 531-5.
7. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am J Gastroenterol* 2001; 96: 2718-23.
8. Hartmann IJ, Groeneweg M, Quero JC, et al. The prognostic significance of subclinical hepatic encephalopathy. *Am J Gastroenterol* 2000; 95: 2029-34.
9. Li YY, Nie YQ, Sha WH, et al. Prevalence of subclinical hepatic encephalopathy in cirrhotic patients in China. *World J Gastroenterol* 2004; 10: 2397-401.
10. Groeneweg M, Quero JC, De Bruijn I, et al. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998; 28: 45-9.
11. Wein C, Koch H, Popp B, Oehler G, Schauder P. Minimal hepatic encephalopathy impairs fitness to drive. *Hepatology* 2004; 39: 739-45.
12. Romero-Gomez M, Grande L, Camacho I. Prognostic value of altered oral glutamine challenge in patients with minimal hepatic encephalopathy. *Hepatology* 2004; 39: 939-43.
13. Romero-Gomez M, Grande L, Camacho I, Benitez S, Irles JA, Castro M. Altered response to oral glutamine challenge as prognostic factor for overt episodes in patients with minimal hepatic encephalopathy. *J Hepatol* 2002; 37: 781-7.
14. Amodio P, Del Piccolo F, Marchetti P, et al. Clinical features and survivial of cirrhotic patients with subclinical cognitive alterations detected by the number connection

test and computerized psychometric tests. *Hepatology* 1999; 29: 1662-7.
15. Dhiman RK, Kurmi R, Thumburu KK, et al. Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver. *Dig Dis Sci* 2010; 55: 2381-90.
16. Bajaj JS, Etemadian A, Hafeezullah M, Saeian K. Testing for minimal hepatic encephalopathy in the United States: An AASLD survey. *Hepatology* 2007; 45: 833-4.
17. McCrea M, Cordoba J, Vessey G, Blei AT, Randolph C. Neuropsychological characterization and detection of subclinical hepatic encephalopathy. *Arch Neurol* 1996; 53: 758-63.
18. Romero Gomez M, Cordoba J, Jover R, et al. Normality tables in the Spanish population for psychometric tests used in the diagnosis of minimal hepatic encephalopathy. *Med Clin* 2006; 127: 246-9.
19. Sharma P, Sharma BC, Puri V, Sarin SK. Critical flicker frequency: diagnostic tool for minimal hepatic encephalopathy. *J Hepatol* 2007; 47: 67-73.
20. Sharma P, Sharma BC, Sarin SK. Critical flicker frequency for diagnosis and assessment of recovery from minimal hepatic encephalopathy in patients with cirrhosis. *Hepatobiliary Pancreat Dis Int* 2010; 9: 27-32.
21. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology* 2002; 35: 357-66.
22. Romero-Gomez M, Cordoba J, Jover R, et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. *Hepatology* 2007; 45: 879-85.
23. Romero-Gomez M. Critical flicker frequency: it is time to break down barriers surrounding minimal hepatic encephalopathy. *J Hepatol* 2007; 47: 10-1.
24. Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology* 1977; 72: 573-83.
25. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Hepatology* 2004; 39: 1441-9.
26. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *Hepatology* 2002; 36: 479-97.
27. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology* 2006; 43: 682-9.
28. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; 29: 664-9.
29. Secretaría de Educación Pública. Educación por niveles. 2010 (Accessed 1 de Julio, 2010). Available from: http://www.sep.gob.mx/wb/sep1/educacion_por_niveles
30. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology* 2007; 45: 549-59.
31. Groeneweg M, Moerland W, Quero JC, Hop WC, Krabbe PF, Schalm SW. Screening of subclinical hepatic encephalopathy. *J Hepatol* 2000; 32: 748-53.
32. Mendez-Sanchez N, Villa AR, Chavez-Tapia NC, et al. Trends in liver disease prevalence in Mexico from 2005 to 2050 through mortality data. *Ann Hepatol* 2005; 4: 52-5.
33. Jover R, Company L, Gutierrez A, et al. Minimal hepatic encephalopathy and extrapyramidal signs in patients with cirrhosis. *Am J Gastroenterol* 2003; 98: 1599-604.
34. Reichenbach A, Fuchs U, Kasper M, el-Hifnawi E, Eckstein AK. Hepatic retinopathy: morphological features of retinal glial (Muller) cells accompanying hepatic failure. *Act Neuropathol* 1995; 90: 273-81.