Original Article

Minimal Hepatic Encephalopathy in Patients with Cirrhosis by Measuring Liver Stiffness and Hepatic Venous Pressure Gradient

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ABSTRACT

Background/Aim: Transient elastography (TE) of liver and hepatic venous pressure gradient (HVPG) allows accurate prediction of cirrhosis and its complications in patients with chronic liver disease. There is no study on prediction of minimal hepatic encephalopathy (MHE) using TE and HVPG in patients with cirrhosis. **Patients and Methods**: Consecutive cirrhotic patients who never had an episode of hepatic encephalopathy (HE) were enrolled. All patients were assessed by psychometry (number connection test (NCT-A and B), digit symbol test (DST), serial dot test (SDT), line tracing test (LTT)), critical flicker frequency test (CFF), TE by FibroScan and HVPG. MHE was diagnosed if there were two or more abnormal psychometry tests (± 2 SD controls). **Results:** 150 patients with cirrhosis who underwent HVPG were screened; 91 patients (61%, age 44.0 ± 11.4 years, M:F:75:16, Child's A:B:C 18:54:19) met the inclusion criteria. Fifty three (58%) patients had MHE (Child A (7/18, 39%), Child B (32/54, 59%) and Child C (14/19, 74%)). There was no significant difference between alanine aminotranferease (ALT), aspartate aminotransferase (AST) and total bilirubin level in patients with MHE versus non MHE. Patients with MHE had significantly lower CFF than non MHE patients (38.4 ± 3.0 vs. 40.2 ± 2.2 Hz, $P = 0.002$). TE and HVPG in patients with MHE did not significantly differ from patients with no MHE (30.9 ± 17.2 vs. 29.8 ± 18.2 KPas, $P = 0.78$; and 13.6 ± 2.7 vs. 13.6 ± 3.2 mmHg, $P = 0.90$, respectively).There was significant correlation of TE with Child's score (0.25, $P = 0.01$), MELD (0.40, $P = 0.001$) and HVPG (0.72, $P = 0.001$) while no correlation with psychometric tests, CFF and MHE. **Conclusion**: TE by FibroScan and HVPG cannot predict minimal hepatic encephalopathy in patients with cirrhosis.

Key Words: FibroScan, hepatic venous pressure gradient, minimal hepatic encephalopathy

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Minimal hepatic encephalopathy (MHE) is characterized by subtle deficits and psychomotor abnormalities that can only be elicited by specialized psychometric tests.[1] MHE remains an important entity for clinicians to recognize because of its negative impact on a patient's health-related quality of life and association with driving impairment and vehicle accidents.[2-6] MHE has also been associated with an increased rate in the development of overt hepatic encephalopathy (HE) and increased mortality in patients with cirrhosis.[7] Hence, the need of early identification and treatment of MHE exists.

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Liver stiffness (LS) measurement by transient elastography (TE) is a very promising non-invasive method for the diagnosis of fibrosis in chronic liver diseases.[8,9] TE allows accurate prediction of cirrhosis and of its complications in patients with chronic liver disease.[10-13] In a study by Foucher *et al*,[13] with a cut off value of 17.6 kPa, negative and positive predictive values for the diagnosis of cirrhosis were 92% and 91%, respectively. They also established the cut off value for complications of cirrhosis, with a negative predictive value of more than 90%. These cut off values were 27.5 kPa for the presence of oesophageal varices, 37.5 kPa for cirrhosis Child B and C, 49.1 kPa for a past history of ascites, 53.7 kPa for hepatocellular carcinoma, and 62.7 kPa for oesophageal bleeding.

Measurement of hepatic venous pressure gradient (HVPG) is a standard method for the assessment of portal pressure and correlates with the occurrence of its complications. The HVPG clearly reflects portal pressure in cirrhotic portal hypertension (PHT).[14-16] Bureau *et al*,[12] concluded

in their study that HVPG was found to be correlated with LS (rho = 0.858; $P < 0.001$) and inversely correlated with prothrombin index (rho = -0.718; $P < 0.001$). Similarly Vizzutti *et al*,[17] found a strong relationship between LS and HVPG measurements in the overall population ($r = 0.81$, $P < 0.0001$) There is no study to know whether TE by FibroScan and HVPG can predict MHE in patients with cirrhosis. The aim of this study was to assess the predictive value of TE by FibroScan and HVPG in the diagnosis of MHE.

PATIENTS AND METHODS

Patient characteristics

From January 2009 to September 2009, consecutive cirrhotic patients (age 18-70 years) who never had encephalopathy and were planned for HVPG were enrolled. Both the authors had an experience of doing more than 500 HVPG and TE. Cirrhosis was diagnosed on a clinical basis involving laboratory tests, endoscopic evidence, sonographic findings and liver histology if available. The exclusion criteria were history of taking lactulose in the past 6 weeks, previous history of hepatic encephalopathy, alcohol intake during the past 6 weeks, variceal bleed < 6 weeks, hepatocellular carcinoma, previous transjugular intrahepatic portosystemic shunt (TIPS) or shunt surgery, significant co morbid illness such as heart, respiratory, or renal failure and any neurologic diseases such as alzheimer's disease, parkinson's disease and non-hepatic metabolic encephalopathies. Patients on psychoactive drugs, such as antidepressants or sedatives were also excluded. The study was approved by the ethics committee of the institute and informed written consent was taken from every patient before enrolling in the study.

Psychometric testing

All patients underwent a combination of psychometric tests including number connection test-A and B (NCT-A, B), digit symbol test (DST), line tracing test (LTT) and serial dotting test (SDT). These tests were easy to administer and could be performed in 30-40 minutes. In DST subjects have to accurately and quickly transcribe symbols corresponding to numbers looking at a key in a timed manner over ninety seconds. The number of correctly transcribed symbols indicates performance, i.e. a low score means poor performance. In SDT subjects place dot exactly in the centre of ten rows of large circles beginning each row on the left side and work to the right. In line tracing tests subjects need to draw a line between two lines on the paper and must stay between, neither touching nor drawing over the printed lines. The test score is the time required to complete the test, including the time needed to correct any errors. Tests were considered abnormal when test score was more than mean ± 2 SD from the age and education matched controls.[18] MHE was diagnosed if 2 or more psychometric tests were abnormal.[1]

Liver stiffness measurement by FibroScan

After an overnight fasting, patients underwent a complete upper abdomen ultrasound examination. Immediately after, TE was performed using the FibroScan apparatus (Echosens, Paris, France), which consists of a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. Mild amplitude and low-frequency vibrations (50 Hz) are transmitted to the liver tissue, inducing an elastic shear wave that propagates through the underlying liver tissue. The velocity of the wave is directly related to tissue stiffness. The tip of the transducer was covered with a drop of gel and placed perpendicularly in the intercostals space with the patient lying in dorsal decubitus position with the right arm in the maximal abduction. Under control TM and A-mode, the operator chose a liver portion within the right liver lobe at least 6 cm thick, free of large vascular structures and gallbladder. Stiffness was measured on a cylinder of hepatic tissue of 1 cm of diameter and 2 to 4 cm of length. The operator had previously performed at least 100 determinations. The median value of 10 successful acquisitions, expressed in kilopascal (kPa), was kept as representative of the LS measurement. LS measurement failure was recorded when no value was obtained after at least 10 shots (valid shots = 0). The results were considered unreliable in the following circumstances: valid shots fewer than 10, SR less than 60%, or interquartile range/LS measurement greater than 30%.[10] All patients underwent TE on the day of psychometric examinations.

Measurement of critical flicker frequency threshold

Critical flicker frequency (CFF) was done by HEPAtonorm analyzer (Hepatonorm Analyzer; R and R Medi-Business Freiburg GmbH, Freiburg, Germany). It was measured in a quiet, semi-darkened room. Patients were first instructed and trained about the procedure. Flicker frequencies were measured 8 times and the mean value was calculated. Measurement of the CFF thresholds was done by intra foveal stimulation with a luminous diode. Decreasing the frequency of the light pulses from 60 Hz downward, the CFF threshold was determined as the frequency when the impression of fused light turned to a flickering one.[19] CFF was done on the same day of psychometric examination and TE measurement.

Measurement of HVPG

After an overnight fast, HVPG measurement was carried out using a standard procedure. Briefly, under local anesthesia and in a supine position, a venous introducer was placed in the right femoral vein by using the Seldinger technique. Under fluoroscopic guidance, a 7F balloon-tipped Swan Ganz Catheter (Boston Scientific, Natick, MA, USA) was introduced into the main right hepatic vein. FHVP and WHVP were measured using a Nihon Kohden (Tokyo, Japan) hemodynamic monitor with pressure transducers.

Measurements were made in triplicate, and the mean of three readings was taken in every case. If there was a difference of more than 1 mmHg between the readings, all the readings were repeated.[20] HVPG was done within one week of assessment of psychometric tests, CFF and TE.

Blood tests, imaging and biochemical examinations

After overnight fasting, patient venous blood was taken and analyzed for routine liver function tests and hematologic parameters by conventional methods and evaluation of viral markers like hepatitis B and hepatic C. Ultrasound abdomen/computed tomography for liver and spleen size along with doppler study for abdominal vessels was done. All patients underwent upper gastrointestinal endoscopy for screening of esophageal and gastric varices and HVPG within one week of enrollment.

Statistical analysis and data management

Data processing was performed by using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA). Data was expressed as mean ± SD. For a comparison of categorical variables, Chi-square and Fisher's exact tests were used, and for continuous variables, a Mann-Whitney test for unpaired data and a Wilcoxon rank-sum test for paired data were used as appropriate. Correlations between variables were examined with a Pearson correlation. The probability level of $P < .05$ was set for statistical significance.

RESULTS

Between January 2009 to September 2009, 150 patients with cirrhosis underwent HVPG; 91 patients (61%) met the inclusion criteria and were included in the study. The causes of cirrhosis were: alcohol ($n = 24$), chronic hepatitis B ($n = 31$), chronic hepatitis C ($n = 12$), cryptogenic cirrhosis ($n = 18$) and others ($n = 6$). 59 patients (39%) were excluded from the study due to: history of recent alcohol intake ($n = 12$), on lactulose therapy ($n = 14$), renal impairment ($n = 6$), hepatocellular carcinoma ($n = 8$), recent use of drugs affecting psychomotor performance ($n = 6$), severe medical problem ($n = 10$) and not willing for TE and psychometry tests ($n = 3$). The clinical and demographic characteristics of the patients enrolled are shown in Table 1.

Psychometric tests, Critical flicker frequency, FibroScan

The normal values of psychometric tests were derived from group comprising 131 men and 39 women. Mean age of controls was 38.9 ± 12.7 years (range 19-71), and the mean formal education in years was 11.5 ± 3.9 (range 0-18). The normal value for NCT-A was 31 ± 10 seconds, NCT-B 56.0 ± 16 seconds, FCT-A 32 ± 12 seconds, FCT-B 120 ± 39 seconds, SDT 55.0 ± 10 seconds, DST 37 ± 9 seconds and LTT 84 ± 16.0 seconds.[14] All patients underwent NCT-A, B, SDT, LTT and DST without any difficulty. There was no significant difference with regards to age (39.9 ± 12.7 vs. 44.0 ± 11.4 years, $P = 0.07$) and education (11.5 ± 3.9 vs. 10.4 ± 4.2 years, $P = .76$) between control group ($n = 170$) and patients enrolled in this study.

Fifty three patients (58%) were diagnosed as MHE based on two or more abnormal (± 2 SD control) psychometric tests

Table 1: Clinical and demographic profile of patients

Parameters	Patients ($n = 91$)
Age (yr)	44.0 ± 11.4
M:F	75:16
MELD score	13.1 ± 4.7
CTP score	8.0 ± 1.6
Child's Status (A:B:C)	18:54:19
Diuretics N (%)	64 (70)
AST (IU/l), median (range)	56 (16-205)
ALT (IU/l), median (range)	45 (18-320)
Na (mmol/l)	135.0 ± 4.3
Beta blockers N (%)	22 (24)
Variceal size (no: small: large)	4:49:38
MHE, *n* (%)	53 (58)
Transient elastography (kPa)	30.4 ± 17.5
CFF (Hz)	39.2 ± 2.8
HVPG (mmHg)	13.6 ± 2.9

CFF: Critical flicker frequency, MELD: Model for end stage liver disease, CTP: Child-Turcotte-Pugh, AST: Aspartate aminotransferase, ALT: Alanine aminotranferease, MHE: Minimal hepatic encephalopathy, HVPG: Hepatic venous pressure gradient

Table 2: Clinical and demographic profile of patients with MHE versus Non MHE patients

Parameters	MHE ($n = 53$)	Non MHE ($n = 38$)	*P*
Age (yr)	44.8 ± 10.7	43.0 ± 12.4	0.45
Median (range)	45 (24-65)	43 (18-70)	
MELD score	13.7 ± 4.4	12.1 ± 5.1	0.13
Median (range)	13 (6-24)	10.5 (6-25)	
CTP score	8.5 ± 1.3	7.5 ± 1.7	0.04
Median (range)	9 (5-11)	7 (5-11)	
Serum Bilirubin	2.2 ± 1.1	2.6 ± 1.9	0.19
median (range)	2 (0.9-5.0)	2.2 (0.6-9.8)	
AST (IU/l)	55.0 ± 21.0	62.3 ± 34.3	0.21
median (range)	52 (16-121)	56.5 (24-205)	
ALT (IU/l)	47.1 ± 18.8	54.7 ± 27.8	0.13
median (range)	44 (18-111)	46 (19-208)	
Transient elastography (kPa)	30.9 ± 17.2	29.8 ± 18.2	0.78
Median (range)	25 (12-75)	22.7 (12-72)	
CFF (Hz)	38.4 ± 3.0	40.2 ± 2.2	0.002
Median (range)	38 (33-45)	40 (34-45.3)	
HVPG	13.6 ± 2.7	13.6 ± 3.2	0.90
Median (range)	13 (9-22)	13 (9-23)	

CFF: Critical fl icker frequency, MELD: Model for end stage liver disease, CTP: Child-Turcotte-Pugh, AST: Aspartate aminotransferase, ALT: Alanine aminotranferease, MHE: Minimal hepatic encephalopathy, HVPG: Hepatic venous pressure gradient

[Tables 2 and 3]. MHE was present in (7/18, 39%) in Child A, (32/54, 59%) in Child B and (14/19, 74%) in Child C status patients. Patients with MHE had significantly lower CFF than non MHE patients (38.4 ± 3.0 vs. 40.2 ± 2.2 Hz, P = 0.002). TE is not significantly different in patients with MHE versus non MHE (30.9 ± 17.2 vs. 29.8 ± 18.2, P = 0.78). Forty three patients had CFF < 39 Hz and in these patients also TE was not significantly higher than patients with CFF > 39 Hz (32.0 ± 16.6 vs. 29.3 ± 18.2 Hz, P = 0.46). TE could be done in all patients (with medium probe, n = 72 and with XL probe in 19 patients with overall success rate 82% and interquartile range 19%).

Hepatic venous pressure gradient

Mean HVPG in all patients was 13.6 ± 2.9 mmHg; Child's A (n = 18, 12.0 ± 3.0 mmHg), Child's B (n = 54, 13.7 ± 2.4 mmHg) and Child's C (n = 19, 14.8 ± 3.6 mmHg). Patients with large varices (n = 38) had significantly higher HVPG than patients with small varices (n = 49): 14.8 ± 3.2 vs. 12.4 ± 2.1 mmHg, P = 0.001. Patients who had bled (n = 31) in the past had significantly higher HVPG than non-bleeders (n = 60): 16.2 ± 2.4 vs. 12.2 ± 2.2 mmHG, P = 0.001. Patients diagnosed as having MHE (n = 53) did not have significantly different HVPG than non MHE patients (n = 38): 13.6 ± 2.7 vs. 13.6 ± 3.2 mmHg, P = 0.90.

FibroScan correlations

There was significant correlation between TE by FibroScan and Child's score (0.25, P = 0.01), MELD (0.40, P = 0.001) and HVPG (0.72, P = 0.001) and no correlation could be found between TE and psychometric tests, CFF and MHE [Table 3].

Table 3: Psychometry tests in patients with MHE versus non MHE

Parameters	MHE (n = 53)	Non MHE (n = 38)	P
NCT-A (sec)	74.1 ± 27.3	37.3 ± 16.1	0.001
NCT-B (sec)	159.4 ± 27.4	77.0 ± 22.2	0.001
SDT (sec)	116.1 ± 58.0	70.1 ± 17.9	0.01
DST (score)	18.5 ± 8.6	30.9 ± 10.7	0.01
LTT (sec)	158.3 ± 58.5	124.5 ± 50.9	0.01

MHE: Minimal hepatic encephalopathy, NCT: Number Line tracing test

Table 4: Correlation with various psychometry tests, CFF and HVPG

Parameters	R	P
NCT-A	0.02	0.83
NCT-B	0.10	0.32
SDT	0.07	0.49
DST	-0.04	0.70
LTT	0.13	0.19
CFF	-0.07	0.45
CTP Score	0.25	0.01
MELD	0.40	0.001
HVPG	0.72	0.001
MHE	0.02	0.78

CFF: Critical fl icker frequency, HVPG: Hepatic venous pressure gradient, NCT: Number connection test, SDT: Serial dot test, DST: Digit symbol test, LTT: Line tracing test, CTP: Child-Turcotte-Pugh, MELD: Model for end stage liver disease, MHE: Minimal hepatic encephalopathy

DISCUSSION

The results of the present study, conducted in a large cohort of patients with cirrhosis, showed that TE and HVPG cannot predict MHE in patients with cirrhosis. TE showed correlation with Child's score, MELD score and HVPG but it is not correlated with MHE. TE and HVPG in patients with MHE were not significantly different from TE and HVPG in non MHE patients [Table 4].

MHE is characterized by subtle deficits and psychomotor abnormalities that can only be elicited by specialized psychometric tests.[1,4] Currently, psychometry tests are commonly used for its diagnosis and CFF is considered an important new diagnostic tool for MHE diagnosis.[1,4,19] MHE was seen in 58% of our patients which correlates with previous studies and we found more patients in Child's C having MHE when compared to Child B and A status.[2-6]

TE (FibroScan) is a non-invasive method proposed for the assessment of hepatic fibrosis in patients with chronic liver disease by measuring liver stiffness. It can be easily performed at the bedside or in the out patients clinic with immediate results and good reproducibility.[10,11] The high reproducibility of liver stiffness measurement has recently been reported together with a low rate of failure.[12,13] TE though is a useful tool to assess fibrosis non-invasively, it is not widely available in many countries. In a recent prospective study, the frequency and determinants of LS failure and unreliable results over a 5-year period, based on 13,369 examinations were related to obesity, particularly increased waist circumference, and limited operator experience.[10] However, the new XL probe provides a higher rate of LSM than the M probe in patients with an increased BMI and shows promising results for the evaluation of liver fibrosis.[21] In our study also we needed XL probe in 19 patients and we could do TE by FibroScan in all patients. Several reports have shown that liver stiffness, measured by TE accurately predicts liver fibrosis in patients with various etiologies of chronic liver diseases.[22,23] However, it must be kept in mind that LS value is influenced by several specific conditions such as acute hepatitis[24,25] and cholestasis.[26] However, in this study we did not find any difference in ALT, AST and total bilirubin level in patients with MHE versus non MHE, although Child's score was higher in MHE patients while there was no difference with regards to MELD score which could be due to lack of ascites component and inclusion of serum creatinine in MELD scoring system. However, this

was not the primary outcome of this study and we could not exclude type II error in interpretation of these results. In a recent study by Robic *et al*,[27] within the 2 year follow-up, 41 patients developed at least one liver disease related complication including HE. The performances of LS for predicting the occurrence of these complications were 0.837 (0.754 -0.920), and majority of these patients had TE > 21.1 kPa. In our study patients with MHE had TE 30.9 ± 17.2 kPa but this did not differentiate patients with MHE versus non MHE patients. TE correlates with CTP and MELD score but not with CFF and MHE in this study. So measuring TE could predict complications related to cirrhosis but not MHE, therefore it has to be evaluated by means of currently available methods like psychometric tests.

HVPG has been shown to be an accurate prognostic index in patients with cirrhosis. An HVPG ≥ 10 mmHg represents clinically significant PHT and predicts development of complications of cirrhosis including death. HVPG > 12 mmHg is the threshold level for variceal rupture. However, no previously published studies evaluated MHE and its association with MHE. LS correlated with HVPG in several studies and therefore, LS was able to detect the presence of significant PHT.[12,28,29] In this study mean HVPG was more than 10 mmHg and patients in Child's B and C had significantly higher HVPG than Child's A patients. Similarly bleeders had higher HVPG than non bleeder. We also found a good correlation between TE and HVPG but HVPG could not predict MHE in patients with cirrhosis which again emphasizes that MHE needs to be evaluated by currently available methods.

CFF is a well-established neurophysiological technique to detect a broad spectrum of neurophysiological abnormalities ranging from visual signal processing (retinal gliopathy) to cognitive functions and CFF < 38 Hz was predictive of further bouts of overt HE.[19,30,31] CFF is a reproducible parameter with little bias for training effects, education, age, daytime, or inter examiner variability.[30,31] Taking a cut off of 39 Hz as MHE by Kircheis *et al*.[30] we did not find any difference in TE in patients with CFF < 39 Hz versus those with CFF ≥ 39 Hz (32.0 ± 16.6 vs. 29.3 ± 18.2 Hz, $P = 0.46$). The nature of the cause of cirrhosis is primordial in the choice of a stiffness cut-off for the diagnosis of cirrhosis using the FibroScan, since the distribution of hepatic fibrosis differs for viral, alcoholic and non-alcoholic liver diseases, and biliary tract conditions[32-34] and this could also affect the prevalence of MHE at same cutoff in patients with different cause of cirrhosis. Hence, MHE which affects patient's quality of life and predicts overt HE need to be evaluated still with conventional methods like psychometric tests and CFF for its detection in patients with cirrhosis and newer modalities like TE and HVPG should not be the sole method to evaluate complications related to cirrhosis. To the best of our knowledge this is the first study evaluating the role of TE and HVPG in predicting MHE in patients with cirrhosis and we did not find that TE and HVPG can predict MHE in cirrhosis.

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