

Prospective Study

Reversibility of minimal hepatic encephalopathy following liver transplantation in Egyptian cirrhotic patients

Mahmoud A Osman, Moataz M Sayed, Khaled A Mansour, Shereen A Saleh, Wesam A Ibrahim, Sara M Abdelhakam, Mohamed Bahaa, Wael A Yousry, Hosam S Elbaz, Reginia N Mikhail, Azza M Hassan, Ehab H Elsayed, Dalia A Mahmoud

Mahmoud A Osman, Moataz M Sayed, Khaled A Mansour, Shereen A Saleh, Wesam A Ibrahim, Wael A Yousry, Hosam S Elbaz, Reginia N Mikhail, Department of Internal Medicine, Hepatology and Gastroenterology, Faculty of Medicine, Ain Shams University, Cairo 11341, Egypt

Sara M Abdelhakam, Department of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo 11341, Egypt

Mohamed Bahaa, Department of Hepatobiliary Surgery, Faculty of Medicine, Ain Shams University, Cairo 11341, Egypt

Azza M Hassan, Department of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University, Cairo 11341, Egypt

Ehab H Elsayed, Department of Internal Medicine, Hepatology and Gastroenterology, National Research Center, Cairo 11341, Egypt

Dalia A Mahmoud, Department of Neuropsychiatry, Faculty of Medicine, Ain Shams University, Cairo 11341, Egypt

Author contributions: Osman MA and Mahmoud DA contributed equally to this work; Osman MA, Sayed MM, Mansour KA, Saleh SA, Abdelhakam SM, Bahaa M and Mahmoud DA designed the research; Osman MA, Ibrahim WA, Bahaa M, Yousry WA, Elbaz HS, Mikhail RN and Mahmoud DA performed the research; Osman MA, Elbaz HS, Mikhail RN, Elsayed EH, Hassan AM and Mahmoud DA analyzed the data; Sayed MM, Mansour KA, Saleh SA, Ibrahim WA, Abdelhakam SM, Yousry WA and Hassan AM contributed analytic tools; Sayed MM, Saleh SA, Ibrahim WA, Abdelhakam SM and Yousry WA wrote the paper.

Institutional review board statement: This study was reviewed and approved by the Research Ethics Committee of Faculty of Medicine, Ain Shams University Institutional Review Board.

Clinical trial registration statement: This study is registered at (<https://clinicaltrials.gov/show/NCT02767622>). The registration

identification number is (NCT02767622 Unique Protocol ID: 875).

Informed consent statement: All study participants provided written informed consent prior to study enrollment.

Conflict-of-interest statement: None of the authors have any conflicts of interests or any financial disclosures.

Data sharing statement: The technical appendix, statistical code and dataset are available from the corresponding author at saratropical@yahoo.com. The participants gave informed consent for the data sharing.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Sara M Abdelhakam, MD, Assistant Professor of Tropical Medicine, Department of Tropical Medicine, Faculty of Medicine, Ain Shams University, Khalifa El-Maamon St., Abbassia, Cairo 11341, Egypt. saratropical@yahoo.com
Telephone: +20-100-1601548
Fax: +20-22-2598751

Received: May 28, 2016

Peer-review started: May 30, 2016

First decision: July 20, 2016

Revised: August 6, 2016

Accepted: September 13, 2016

Article in press: September 18, 2016

Published online: October 28, 2016

Abstract

AIM

To evaluate the reversibility of minimal hepatic encephalopathy (MHE) following liver transplantation (LT) in Egyptian cirrhotic patients.

METHODS

This prospective study included twenty patients with biopsy-proven liver cirrhosis listed for LT and twenty age- and sex-matched healthy control subjects. All underwent neuro-psychiatric examination, laboratory investigations, radiological studies and psychometric tests including trail making test A (TMT A), TMT B, digit symbol test and serial dotting test. The psychometric hepatic encephalopathy score (PHES) was calculated for patients to diagnose MHE. Psychometric tests were repeated six months following LT in the cirrhotic patient group.

RESULTS

Before LT, psychometric tests showed highly significant deficits in cirrhotic patients in comparison to controls ($P < 0.001$). There was a statistically significant improvement in test values in the patient group after LT; however, their values were still significantly worse than those of the controls ($P < 0.001$). The PHES detected MHE in 16 patients (80%) before LT with a median value of -7 ± 3.5 . The median PHES value was significantly improved following LT, reaching -4.5 ± 5 ($P < 0.001$), and the number of patients with MHE decreased to 11 (55%). The pre-transplant model for end-stage liver disease (MELD) score ≥ 15 was significantly related to the presence of post-transplant MHE ($P = 0.005$). More patients in whom reversal of MHE was observed had a pre-transplant MELD score < 15 .

CONCLUSION

Reversal of MHE in cirrhotic patients could be achieved by LT, especially in those with a MELD score < 15 .

Key words: Liver transplantation; Model for end-stage liver disease score; Psychometric tests; Minimal hepatic encephalopathy; Cirrhosis

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We evaluated the reversibility of minimal hepatic encephalopathy (MHE) following liver transplantation (LT) in Egyptian cirrhotic patients. Twenty patients with biopsy-proven liver cirrhosis listed for LT and twenty age- and sex-matched healthy controls were included. All underwent psychometric tests including trail making test A, trail making test B, digit symbol test and serial dotting test. Psychometric hepatic encephalopathy score was calculated for patients to diagnose MHE. Psychometric tests were repeated six months following LT in the cirrhotic patient group. We found that the reversal of MHE could be achieved by LT especially in those with a model for end-stage liver disease score < 15 .

Osman MA, Sayed MM, Mansour KA, Saleh SA, Ibrahim WA, Abdelhakam SM, Bahaa M, Yousry WA, Elbaz HS, Mikhail RN, Hassan AM, Elsayed EH, Mahmoud DA. Reversibility of minimal hepatic encephalopathy following liver transplantation in Egyptian cirrhotic patients. *World J Hepatol* 2016; 8(30): 1279-1286 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i30/1279.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i30.1279>

INTRODUCTION

The prevalence of overt hepatic encephalopathy (HE) in patients with decompensated liver cirrhosis ranges from 16% to 21%, while that of minimal HE (MHE) or covert HE is 20%-80%^[1].

MHE impairs daily functioning, driving performance, work capability and learning ability in cirrhotic patients. It also predisposes to overt HE and increased mortality^[2]. There are several methods of diagnosing MHE, such as comprehensive neuropsychological examinations, standard psychometric batteries, and computerized testing^[3].

The psychometric hepatic encephalopathy score (PHES) battery can detect neuropsychiatric abnormalities and MHE. It assesses visual perception, construction, visual/spatial orientation, motor speed and accuracy, concentration, and attention in cirrhotic patients with end-stage liver disease. When PHES was compared to the standard methods of determining HE, its sensitivity and specificity were 96% and 100%, respectively^[4].

The PHES was initially composed of seven tests. The portosystemic encephalopathy battery was introduced later to exclude tests with poor sensitivity. It includes the line tracing test (LTT) and/or the digit symbol test, in addition to the number connection tests A and B (NCT A and B)^[5]. The sum of the scores of these tests ranges between +5 and -15. A score of below or equal to -4 is diagnostic for MHE^[4].

The LTT requires the longest time to calculate its score, and there is an existing controversy in interpretation of its two outcomes: Time and errors. Thus, only three of the four tests, NCT-A, NCT-B and DST, have been commonly used for MHE detection^[6]. The result of any test was regarded to be abnormal if it was beyond the 2 standard deviation range of the control subjects. In some previous studies, MHE was diagnosed when two of these tests were abnormal^[7]. In others, it was diagnosed when only one test was abnormal^[8].

Liver transplantation (LT) is now considered an established effective and innovative treatment option for patients with end-stage liver diseases for a wide range of indications over the last fifty years^[9]. The surgical outcomes and survival rates following LT have been previously estimated; however, the effect of LT on MHE has not been properly studied. A few studies have compared the cognitive performance of cirrhotic patients before and after LT. Some demonstrated cognitive improvement, and others have suggested reversibility of MHE after LT^[10,11].

This study aimed to evaluate the reversibility of MHE following liver transplantation in Egyptian cirrhotic patients.

MATERIALS AND METHODS

This prospective study was conducted at Ain Shams Center for Organ Transplant, Ain Shams Specialized Hospital, Cairo, Egypt from June 2014 to April 2015. It included twenty right-handed patients with biopsy-proven liver cirrhosis listed for LT.

In addition, twenty age- and sex-matched healthy persons were enrolled, constituting the control group. The groups were similar regarding number of education years and handedness. The healthy controls were collected from the outpatient clinics among those coming for pre-employment screenings. Liver and systemic diseases were excluded by history, physical examination, laboratory and radiologic assessment.

Written informed consent was obtained from patients and controls prior to inclusion in the study. The study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients' selection

Exclusion criteria: (1) patients with clinical or laboratory evidence of any concomitant infection, severe gastrointestinal bleeding, anemia, electrolyte abnormalities, or renal insufficiency; (2) overt hepatic encephalopathy (persistent or episodic) as revealed by a standard clinical neurological examination; (3) significant cortical atrophy or other structural brain changes as revealed by conventional neurological imaging studies; (4) regular use of psychotropic drugs, such as benzodiazepines; (5) known major psychiatric disorder; (6) patients unable to perform the tests (illiterate or with upper limb motor handicaps); (7) less than 6 mo of complete alcohol abstinence; and (8) post-transplant toxic levels of immunosuppressive drugs.

All of the following were performed to recruited patients and controls: (1) full history taking together with a full clinical, neurological and psychiatric examination done by both an experienced hepatologist and neuropsychiatrist; (2) laboratory investigations including complete blood count; liver function tests: Alanine transaminase, aspartate transaminase, total and direct bilirubin, international normalized ratio (INR), prothrombin time, serum albumin; kidney function tests and full electrolytes including blood urea nitrogen, creatinine, sodium, potassium, magnesium, calcium, phosphorus; C-reactive protein to exclude patients with any infections; and post-transplant immunosuppressive drug levels for patients only to exclude those with toxic levels. The modified Child-Pugh score was calculated for patients, and each patient was categorized as A, B or C. Additionally, the model for end-stage liver disease (MELD) score was calculated for patients using laboratory results collected immediately before LT with no adjustments

for malignancy. We calculated the MELD score using the following formula: $MELD = [0.957 \times \ln(\text{creatinine mg/dL}) + 0.378 \times \ln(\text{bilirubin mg/dL}) + 1.12 \times \ln(\text{INR}) + 0.643 \times 10^8]$; (3) radiological studies included pelvi-abdominal ultrasound with examination of liver size, echogenicity, splenomegaly, amount of ascites, portal vein diameter and patency, presence of any hepatic focal lesions or any abdominal malignancy and a detailed kidney examination pre- and post-transplantation (Hitachi, EUB-5500). A computerized tomography (CT) for the brain was performed to all patients to exclude any brain pathology (Toshiba, High Speed 16 Slice); and (4) psychometric tests included the following neuropsychological tests.

Trail making test A: Patient should draw a line from number (1) to number (2) and from (2) to number (3) till reaching number (24), without elevating the pencil from the paper. The time was recorded in seconds. If the patient made an error, the examiner told him to correct it, but the timing was not stopped. The average score was 29 s, while the deficient score was > 78 s and the rule of thumb was that most completed it in 90 s. The rule of thumb is a broadly accurate guide or principle, based on practice rather than theory^[12,13].

Trail making test B: Patient should draw a line from number (1) to letter (A), then from letter (A) to number (2), then from number (2) to letter (B), and so on, alternating the number and letter respecting the alphabetical order till letter (L). After explaining the test to the patient, timing should be started and recorded in seconds, including time needed to correct any error done. The average score was 75 s, while > 273 s was considered deficient and the rule of thumb was that most completed it in 3 min.

Digit symbol (substitution) test: A coding key was presented consisting of nine abstract symbols, each paired with a number. The patient was required to scan the key and write down the symbol corresponding to each number as rapidly as possible. Ninety seconds were given to the patient and when the time was finished, the number of symbols performed by the patient was counted. The score was recorded in points. If the patient made any errors, timing continued towards their 90 s, and the patient might lose time. A healthy individual should be able to complete the test in 90 s or less. A fall of 1 to 1.5 SD below the mean is considered suggestive of cerebral dysfunction.

Serial dotting test: Also called the circle dotting test, the serial dotting test (SDT) was used to test pure motor speed. The patient was asked to put a dot in each of the 100 circles given on the sheet after being prepared first by dotting the 20 circles at the top of the sheet.

The results of the trail making test A (TMT A), TMT B, and SDT were measured in seconds, including the time needed to correct any errors, and the results of digit symbol (substitution) test (DST) were measured as

points.

Accordingly, a better performance was reflected by a higher result of DST and lower results of other tests.

Interpretation of the score: To obtain the measure of overall visual-motor and visual-constructive performance, we calculated the average percentile score of the 4 selected tests: TMT A, TMT B, DST and SDT. The average score of these tests was arbitrarily named the visual-motor and visual-constructive performance (VMCP) score or PHES. The patient was diagnosed to have MHE when his total score was equal or below -4.

Post-transplantation follow-up

The immunosuppressive regimen included cyclosporine or tacrolimus, mycophenolate mofetil (MMF), and corticosteroids in all patients except those transplanted for hepatocellular carcinoma (HCC). In patients transplanted for HCC, the regimen included calcineurin inhibitors and steroids only. Trough levels of cyclosporine were maintained between 200 and 300 ng/mL while those of tacrolimus were maintained between 8 and 12 ng/mL. Rapid withdrawal of corticosteroids within three months was routine in all patients.

In cases of acute rejection, the first-line therapy consisted of optimization of the maintenance level of immunosuppression. If there was no response, then MMF or rapamycin were added to the patient's regimen, if not already being taken. In some cases, a shift from cyclosporine to tacrolimus was beneficial. A small dose of steroids was used if all other measures failed.

The complete psychometric battery was repeated six months following LT in the cirrhotic patient group. The post-transplant testing was done while the patient was in a stable condition with no clinical or laboratory evidence of any concomitant infection, anemia, electrolyte abnormalities, acute transplant rejection episode or other severe clinical problems.

Statistical analysis

Data were analyzed using the SPSS software computer program version 18 (SPSS, Chicago, IL, United States). They were described as the mean \pm standard deviation (SD) for quantitative (parametric) variables and as median \pm inter-quartile range (IQR) for quantitative (non-parametric) variables. Qualitative (categorical) variables were presented as frequency and percentage. The independent samples *t*-test was used for the comparison of quantitative parametric variables among two independent groups and the Mann Whitney *U* test was used for non-parametric data. The Wilcoxon Signed Ranks test was used for the comparison of quantitative non-parametric variables among two dependent groups (before and after transplantation). The χ^2 test (or Fisher's exact test when appropriate) was used for comparison of distribution of qualitative variables among different groups.

Significance level (*P*) value: (1) $P \leq 0.05$ was significant; (2) $P < 0.01$ was highly significant; and (3) $P >$

0.05 was non-significant.

The statistical methods of this study were reviewed by Azza M Hassan, Department of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

RESULTS

This prospective study included twenty patients with biopsy-proven hepatitis C virus (HCV)-related liver cirrhosis listed for LT. Their mean age was 53.2 ± 5.39 years and they consisted of 17 males (85%) and 3 females (15%). Five patients were diagnosed with hepatocellular carcinoma on top of liver cirrhosis.

In addition, twenty age- and sex-matched healthy subjects were enrolled, constituting the control group. Their mean age was 53.4 ± 6.49 years and they consisted of 15 males (75%) and 5 females (25%).

Before LT, the median \pm IQR of Child-Pugh score of the enrolled patients was 9 ± 4.5 ; five patients (25%) were Child A, six (30%) were B and nine (45%) patients were Child C. Their median \pm IQR of MELD score was 14.5 ± 6.5 , where 50% (10 patients) had a MELD score below 15% and 50% (10 patients) had a MELD score above 15.

Six months following LT, the median \pm IQR of Child-Pugh and MELD scores were 6 ± 1.8 and 11.5 ± 4.5 , respectively, with a statistically significant improvement ($P < 0.001$ and 0.002 , respectively) (Table 1).

Table 2 shows the analysis of the median score values of different psychometric tests (TMT A, TMT B, DST and SDT) and the VMCP score in patients before and after LT, as well as in healthy control subjects. Before LT, the psychometric tests and the VMCP score showed highly significant deficits in cirrhotic patients in comparison to controls ($P < 0.001$).

After LT, there were statistically significant improvements in test values in the patient group when compared to their values before LT. However, the values of patients after LT were still significantly worse than those of the control subjects ($P < 0.001$).

Among the studied 20 cirrhotic patients, the PHES, represented by the VMCP score, detected MHE in 16 patients (80%) before LT, with a median value of -7 ± 3.5 . The median PHES value was significantly improved following LT, reaching -4.5 ± 5 ($P < 0.001$), and the number of patients with MHE decreased to 11 (55%) post-LT.

Table 3 shows that the pre-transplant MELD score ≥ 15 was significantly related to the presence of post-transplant MHE ($P = 0.005$). In cirrhotic patients with a pre-transplant MELD score ≥ 15 , 100% had pre-transplant MHE and 90% had post-transplant MHE. On the other hand, among those with a MELD score < 15 , 60% had pre-transplant MHE and 20% had post-transplant MHE. A higher number of patients in whom reversal of MHE was observed had a pre-transplant MELD score < 15 .

Table 1 Laboratory data, Child-Pugh and model for end-stage liver disease scores before and after liver transplantation in the patients' group

Variable	Before LT (median ± IQR)	After LT (median ± IQR)	Z	P value
INR	1.5 ± 0.6	1.4 ± 0.4	2.198	0.029 ¹
ALT (N: 7-40 IU/L)	24.5 ± 35.25	19.5 ± 29.8	2.201	0.026 ¹
AST (N: 7-37 IU/L)	44.5 ± 28	22.5 ± 13.75	2.918	0.002 ²
Total bilirubin (N: 0.2-1.2 mg/dL)	2 ± 2.45	1.4 ± 0.8	2.156	0.029 ¹
Albumin (N: 3.5-5.3 g/dL)	2.3 ± 1.15	3.3 ± 0.9	3.021	0.021 ¹
Creatinine (N: 0.5-1.2 mg/dL)	0.9 ± 0.4	1 ± 0.2	0.176	0.893
BUN (N: 20-40 mg/dL)	12 ± 6.8	11.5 ± 4.8	0.218	0.839
Sodium (N: 135-147 mEq/L)	132.5 ± 11.75	134.5 ± 10.8	0.197	0.856
Potassium (N: 3.5-5.3 mEq/L)	3.8 ± 0.7	4.4 ± 0.8	2.469	0.011 ¹
Calcium (N: 9-11 mg/dL)	8.6 ± 1.1	8.9 ± 1.3	2.584	0.007 ²
Phosphorus (N: 3-4.5 mg/dL)	3.2 ± 0.6	3.6 ± 1.3	3.219	< 0.001 ²
Magnesium (N: 1.8-3.6 mg/dL)	2.1 ± 0.6	2.2 ± 0.7	1.777	0.076
Child-Pugh score	9 ± 4.5	6 ± 1.8	3.549	< 0.001 ²
MELD score	14.5 ± 6.5	11.5 ± 4.5	2.928	0.002 ²

¹Significant; ²Highly significant. Z: Wilcoxon signed ranks test; IQR: Inter-quartile range; INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; MELD: Model for end-stage liver disease; LT: Liver transplantation; N: Normal range.

Table 2 Median score values of different psychometric tests in controls and patients before and after liver transplantation

	Controls	Patients before LT	Patients after LT	Patients before LT vs after LT (P value) ¹	Controls vs patients before LT (P value) ²	Controls vs patients after LT (P value) ²
TMT A (median ± IQR)	27 ± 8	110 ± 32.5	80 ± 30.8	0.010	< 0.001	< 0.001
TMT B (median ± IQR)	62 ± 17.3	282.5 ± 137.5	167.5 ± 72.0	0.002	< 0.001	< 0.001
DST (median ± IQR)	60 ± 4.75	22 ± 6	28.5 ± 14.5	0.001	< 0.001	< 0.001
SDT (median ± IQR)	34 ± 3.75	62 ± 20.75	51 ± 27.5	0.002	< 0.001	< 0.001
VMCP (median ± IQR)	1 ± 1	-7 ± 3.5	-4.5 ± 5.0	< 0.001	< 0.001	< 0.001

¹Wilcoxon signed ranks test; ²Mann Whitney U test. TMT: Trail making test; DST: Digit symbol test; SDT: Serial dotting test; VMCP: Visual-motor and visual-constructive performance score; LT: Liver transplantation; IQR: Inter-quartile range.

Table 3 Relation between pre-transplant model for end-stage liver disease score and the presence of pre- and post-transplant minimal hepatic encephalopathy n (%)

		Pre-transplant MELD score		χ^2	P value
		< 15 (n = 10)	≥ 15 (n = 10)		
Pre-transplant	-ve	4 (40)	0 (0)	5.000 ¹	0.087
MHE	+ve	6 (60)	10 (100)		
Post-transplant	-ve	8 (80)	1 (10)	9.899 ¹	0.005 ²
MHE	+ve	2 (20)	9 (90)		

¹Fisher's exact test; ²Highly significant. MELD: Model for end-stage liver disease; MHE: Minimal hepatic encephalopathy; -ve: Negative; +ve: Positive.

Table 4 shows comparison between patients who recovered from MHE ($n = 5$) and those who didn't recover ($n = 11$) regarding age, sex, pre-transplant lab investigations and pre-transplant Child and MELD scores. We found that non-recovered patients had significantly higher INR, total bilirubin, Child and MELD scores than recovered ones ($P = 0.027, 0.013, 0.038$ and 0.009 , respectively).

DISCUSSION

In the current study, twenty cirrhotic patients listed for

LT and twenty healthy controls were included. Patients with pre or post-transplant clinical or laboratory evidence of infection, electrolyte imbalance, renal impairment or immunosuppressive drugs toxicity were excluded from the study. The etiology of liver cirrhosis in the included patients was chronic hepatitis C. Egypt has the highest prevalence of HCV worldwide, with an exceptionally high burden of liver disease^[14].

A neuropsychological test battery, consisting of TMT A, TMT B, SDT and DST was applied to both the cirrhotic patient and control groups before and six months after LT. These are the same tests used by Wang *et al.*^[3] and Tsai *et al.*^[15] to diagnose MHE. They have high sensitivity and specificity and are easily applied with no difficulty in their score calculation^[15,16]. These tests monitor changes in attention, motor speed and executive functions, which are the first to improve in the post transplantation period^[3,16]. The TMT is a measure of attention, speed, and mental flexibility. It also tests spatial organization, visual pursuits, recall, and recognition^[12]. Part A tests visual scanning, numeric sequencing, and visuo-motor speed, while part B tests cognitive demands including visual motor, visual spatial abilities and mental flexibility^[16,17]. The DST measures the perceptual ability^[18], while the SDT tests the pure motor speed^[19].

The total score of the four tests (TMT A, TMT B, SDT

Table 4 Comparison between recovered and non-recovered patients regarding age, sex, pre-transplant laboratory investigations and pre-transplant Child and model for end-stage liver disease scores

Variable	Recovered (<i>n</i> = 5) (median ± IQR)	Non-recovered (<i>n</i> = 11) (median ± IQR)	Z ¹	P value
INR	1.5 ± 0.5	1.7 ± 0.5	2.231	0.027
ALT	25 ± 51	38 ± 36	0.397	0.743
AST	49 ± 45.5	53 ± 39	0.283	0.827
Total bilirubin	1.4 ± 1	3.1 ± 2.9	2.437	0.013
Albumin	2.3 ± 1	2.3 ± 0.5	1.208	0.267
Creatinine	0.7 ± 0.5	0.9 ± 0.4	0.517	0.661
BUN	11 ± 11.5	12 ± 5	0.514	0.636
Sodium	139 ± 12.5	132 ± 7	0.910	0.377
Potassium	4 ± 1.2	3.6 ± 0.8	1.310	0.221
Calcium	8.9 ± 0.7	8.3 ± 1.3	0.746	0.482
Phosphorus	2.7 ± 0.8	3.2 ± 1.3	1.204	0.259
Magnesium	2.3 ± 0.6	2 ± 0.6	0.969	0.355
Child-Pugh score	9 ± 1.5	11 ± 1	2.140	0.038
MELD score	13 ± 3.5	17 ± 5	2.557	0.009
Age (mean ± SD)	56.6 ± 1.7	51.2 ± 6.1	1.911 ²	0.077
Sex				
Male (<i>n</i> , %)	4 (80)	9 (81.8)	0.007 ³	1.000
Female (<i>n</i> , %)	1 (20)	2 (18.2)		

¹Mann Whitney *U* test; ²Independent samples *t*-test; ³ χ^2 , Fisher's exact test. INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; MELD: Model for end-stage liver disease; IQR: Inter-quartile range; SD: Standard deviation.

and DST), which represents the VMCP score or PHES, has a cutoff level of -4. Any patient with a score below or equal to -4 is defined as having MHE^[3,15,16].

With regard to the scores of TMT A, TMT B, DST and SDT, and the total PHES score in the current study; significant differences were found between patients and control subjects, together with the significant improvement in the patient scores after LT. This is in agreement with Mattarozzi *et al*^[20].

The significant improvement of the patients' MELD score after LT agrees with Lin *et al*^[10] and Mattarozzi *et al*^[20].

The present study supports the relation between MHE and higher values of a MELD score. This is also in agreement with Mattarozzi *et al*^[20] and Montagnese *et al*^[21]. More patients with a pre-transplant MELD score > 15 experienced pre- and post-transplant MHE. More patients in whom reversal of MHE was observed had a pre-transplant MELD score < 15, indicating that early LT for patients with a MELD score < 15 may be associated with a higher incidence of reversal of MHE and could save the brain from the irreversible damages associated with end-stage liver disease. These findings may change the LT priority for patients with MHE with a MELD score < 15 exceeding priority over those with a MELD > 15.

In a trial to find the factors affecting the reversibility of MHE, comparison between patients who recovered and those who didn't was done in the present study. Pre-transplant Child and MELD scores were significantly lower in patients who recovered from MHE. Age and sex differences were insignificant between those who recovered and those who didn't.

This is different from the study of Mechtcheriakov *et al*^[22], in which the duration of liver cirrhosis and its severity (as determined by the Child classification) did not influence the improvement after LT. However, O'Carroll *et al*^[23] reported that severe liver disease at pre-transplant assessment was associated with more slowing of reaction times and increased bioelectric dysfunction of the brain. In the study of Mechtcheriakov *et al*^[22], patients' age was not related to recovery from MHE after LT which is similar to our study.

Although there was improvement in the cognitive function after LT in the current study, it did not reach the normal optimal levels of the healthy controls. This observation agrees with O'Carroll *et al*^[23], Tarter *et al*^[24] and Garcia-Martinez *et al*^[25] indicating that MHE and the deterioration in cognitive function in liver disease patients are not completely reversible after LT.

It was hypothesized by Rose *et al*^[26] that hepatic encephalopathy may be manifested by either "delirium-like" or "dementia-like" clinical features. The former is likely to be metabolic in origin, whereas the latter is likely to be due to a structural brain lesion, which may be specific to liver disease.

Ammonia has been suggested to have a role in the metabolic pathogenesis of MHE. Hyperammonemia in patients with liver cirrhosis may result in an increase in the brain glutamine with subsequent reduction in the brain magnetization-transfer ratio^[25].

Teperman^[11] demonstrated that patients who survived 10 years post-LT had significant cognitive dysfunction and poor health-related quality of life. This supports the evidence for a "dementia-like" parameter

of MHE that is irreversible after LT. Lin *et al.*^[10] showed improvement of both the extracellular cerebral edema and the demyelination of white matter in patients with MHE following LT, but they still did not reach the control level.

In the current study, gross structural brain lesions were excluded by CT brain before and after LT. Future studies should expand and should include larger sample size in order to investigate different metabolic, neurological and physical tests that could identify the exact causes of incomplete recovery of the brain cognitive functions.

In conclusion, the reversal of minimal hepatic encephalopathy in cirrhotic patients can be achieved by liver transplantation, especially in those with a pre-transplant MELD score < 15.

COMMENTS

Background

Minimal hepatic encephalopathy (MHE) impairs daily functioning, driving performance, work capability and learning ability in cirrhotic patients. It also predisposes to overt hepatic encephalopathy and increases mortality. The psychometric hepatic encephalopathy score (PHES) battery can detect neuropsychiatric abnormalities. It assesses visual perception, construction, visual/spatial orientation, motor speed and accuracy, concentration, and attention in cirrhotic patients with end-stage liver disease. Liver transplantation (LT) is now considered an established effective and innovative treatment option for patients with end-stage liver diseases. The effects of LT on MHE are poorly studied.

Research frontiers

The authors evaluated the reversibility of MHE following LT in Egyptian cirrhotic patients. Twenty right-handed patients with biopsy-proven liver cirrhosis listed for LT and twenty age- and sex-matched healthy control subjects were included. All underwent psychometric tests including trail making test A (TMT A), TMT B, the digit symbol test and the serial dotting test. The PHES was calculated to diagnose MHE. Psychometric tests were repeated six months following LT in cirrhotic patient group. They found that reversal of MHE in cirrhotic patients could be achieved by LT, especially in those with a MELD score < 15.

Innovations and breakthroughs

This is the first Egyptian study that addresses the reversibility of minimal hepatic encephalopathy following LT.

Applications

The findings of this study may represent a future strategy, indicating that early LT for patients with a MELD score < 15 may be associated with a higher incidence of reversal of MHE and could save the brain from the irreversible damage associated with end-stage liver disease.

Terminology

MHE is a neuropsychiatric syndrome that may occur in cirrhotic patients with no recognizable clinical symptoms of hepatic encephalopathy but with mild cognitive and psychomotor deficits, impairing daily functioning.

Peer-review

This study provides very interesting results which indicate that liver transplantation cannot fully recover all Egyptian patients from MHE caused by hepatitis C virus-induced cirrhosis, and has the most beneficial effect in patients with pre-transplant MELD score less than 15. This is the first study that investigated the reversibility of MHE in Egyptian population after liver transplantation, and provides important information regarding the effect of transplantation on the course of MHE.

REFERENCES

- 1 **Jepsen P**, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; **51**: 1675-1682 [PMID: 20186844 DOI: 10.1002/hep.23500]
- 2 **Agrawal S**, Umopathy S, Dhiman RK. Minimal hepatic encephalopathy impairs quality of life. *J Clin Exp Hepatol* 2015; **5**: S42-S48 [PMID: 26041957 DOI: 10.1016/j.jceh.2014.11.006]
- 3 **Wang JY**, Zhang NP, Chi BR, Mi YQ, Meng LN, Liu YD, Wang JB, Jiang HX, Yang JH, Xu Y, Li X, Xu JM, Zhang G, Zhou XM, Zhuge YZ, Tian DA, Ye J, Liu YL. Prevalence of minimal hepatic encephalopathy and quality of life evaluations in hospitalized cirrhotic patients in China. *World J Gastroenterol* 2013; **19**: 4984-4991 [PMID: 23946605 DOI: 10.3748/wjg.v19.i30.4984]
- 4 **Ly XF**, Liu K, Qiu YW, Cai PQ, Li J, Jiang GH, Deng YJ, Zhang XL, Wu PH, Xie CM, Wen G. Anomalous gray matter structural networks in patients with hepatitis B virus-related cirrhosis without overt hepatic encephalopathy. *PLoS One* 2015; **10**: e0119339 [PMID: 25786256 DOI: 10.1371/journal.pone.0119339]
- 5 **Nabi E**, Bajaj JS. Useful tests for hepatic encephalopathy in clinical practice. *Curr Gastroenterol Rep* 2014; **16**: 362 [PMID: 24357348 DOI: 10.1007/s11894-013-0362-0]
- 6 **Riggio O**, Ridola L, Pasquale C, Pentassuglio I, Nardelli S, Moscucci F, Merli M, Montagnese S, Amodio P, Merkel C. A simplified psychometric evaluation for the diagnosis of minimal hepatic encephalopathy. *Clin Gastroenterol Hepatol* 2011; **9**: 613-616.e1 [PMID: 21440091 DOI: 10.1016/j.cgh.2011.03.017]
- 7 **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 [PMID: 20133225]
- 8 **Marić D**, Klasnja B, Filipović D, Brkić S, Ruzić M, Bugarski V. Minimal hepatic encephalopathy in patients with decompensated liver cirrhosis. *Acta Clin Croat* 2011; **50**: 375-380 [PMID: 22384773]
- 9 **Shukla A**, Vadeyar H, Rela M, Shah S. Liver Transplantation: East versus West. *J Clin Exp Hepatol* 2013; **3**: 243-253 [PMID: 25755506 DOI: 10.1016/j.jceh.2013.08.004]
- 10 **Lin WC**, Chou KH, Chen CL, Chen HL, Lu CH, Li SH, Huang CC, Lin CP, Cheng YF. Longitudinal brain white matter alterations in minimal hepatic encephalopathy before and after liver transplantation. *PLoS One* 2014; **9**: e105887 [PMID: 25166619 DOI: 10.1371/journal.pone.0105887]
- 11 **Teperman LW**. Impact of pretransplant hepatic encephalopathy on liver posttransplantation outcomes. *Int J Hepatol* 2013; **2013**: 952828 [PMID: 24324895 DOI: 10.1155/2013/952828]
- 12 **Gaudino EA**, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? *J Clin Exp Neuropsychol* 1995; **17**: 529-535 [PMID: 7593473 DOI: 10.1080/01688639508405143]
- 13 **Lezak MD**, Howieson DB, Loring DW. *Neuropsychological Assessment*. 4th ed. New York, NY: Oxford University Press, 2004: 1016
- 14 **Lavanchy D**. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011; **17**: 107-115 [PMID: 21091831 DOI: 10.1111/j.1469-0691.2010.03432.x]
- 15 **Tsai CF**, Chu CJ, Huang YH, Wang YP, Liu PY, Lin HC, Lee FY, Lu CL. Detecting minimal hepatic encephalopathy in an endemic country for hepatitis B: the role of psychometrics and serum IL-6. *PLoS One* 2015; **10**: e0128437 [PMID: 26039496 DOI: 10.1371/journal.pone.0128437]
- 16 **Zhang Y**, Feng Y, Cao B, Tian Q. Effects of SIBO and rifaximin therapy on MHE caused by hepatic cirrhosis. *Int J Clin Exp Med* 2015; **8**: 2954-2957 [PMID: 25932262]
- 17 **Reitan RM**. Validity of the Trail Making test as an indicator of organic brain damage. *Percept Mot Skills* 1958; **8**: 271-276 [DOI: 10.2466/PMS.8.7.271-276]
- 18 **Bettcher BM**, Libon DJ, Kaplan E, Swenson R, Penney DL. Digit Symbol Substitution Test. In: *Kreutzer JS, DeLuca J, Caplan B. Encyclopedia of Clinical Neuropsychology*. New York: Springer,

- 2011: 849-853 [DOI: 10.1007/978-0-387-79948-3_1289]
- 19 **Kharbanda PS**, Saraswat VA, Dhiman RK. Minimal hepatic encephalopathy: diagnosis by neuropsychological and neurophysiologic methods. *Indian J Gastroenterol* 2003; **22** Suppl 2: S37-S41 [PMID: 15025253]
- 20 **Mattarozzi K**, Stracciari A, Vignatelli L, D'Alessandro R, Morelli MC, Guarino M. Minimal hepatic encephalopathy: longitudinal effects of liver transplantation. *Arch Neurol* 2004; **61**: 242-247 [PMID: 14967773 DOI: 10.1001/archneur.61.2.242]
- 21 **Montagnese S**, Balistreri E, Schiff S, De Rui M, Angeli P, Zanusi G, Cillo U, Bombonato G, Bolognesi M, Sacerdoti D, Gatta A, Merkel C, Amodio P. Covert hepatic encephalopathy: agreement and predictive validity of different indices. *World J Gastroenterol* 2014; **20**: 15756-15762 [PMID: 25400460 DOI: 10.3748/wjg.v20.i42.15756]
- 22 **Mechtcheriakov S**, Graziadei IW, Mattedi M, Bodner T, Kugener A, Hinterhuber HH, Marksteiner J, Vogel W. Incomplete improvement of visuo-motor deficits in patients with minimal hepatic encephalopathy after liver transplantation. *Liver Transpl* 2004; **10**: 77-83 [PMID: 14755782 DOI: 10.1002/lt.20009]
- 23 **O'Carroll RE**, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver transplantation: a prospective, national, single-center study. *Liver Transpl* 2003; **9**: 712-720 [PMID: 12827558 DOI: 10.1053/jlts.2003.50138]
- 24 **Tarter RE**, Hegedus AM, Van Thiel DH, Edwards N, Schade RR. Neurobehavioral correlates of cholestatic and hepatocellular disease: differentiation according to disease specific characteristics and severity of the identified cerebral dysfunction. *Int J Neurosci* 1987; **32**: 901-910 [PMID: 3596934 DOI: 10.3109/00207458709043346]
- 25 **Garcia-Martinez R**, Rovira A, Alonso J, Jacas C, Simón-Talero M, Chavarria L, Vargas V, Córdoba J. Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume. *Liver Transpl* 2011; **17**: 38-46 [PMID: 21254343 DOI: 10.1002/lt.22197]
- 26 **Rose C**, Jalan R. Is minimal hepatic encephalopathy completely reversible following liver transplantation? *Liver Transpl* 2004; **10**: 84-87 [PMID: 14755783 DOI: 10.1002/lt.20030]

P- Reviewer: McMillin MA, Stanojlovic O **S- Editor:** Gong ZM
L- Editor: A **E- Editor:** Li D





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

