Mohamed *et al.*
Middle East Current Psychiatry (2022) 29:4
https://doi.org/10.1186/s43045-022-00175-3

Middle East Current Psychiatry

RESEARCH Open Access

Cognitive impairment in recipients of liver transplantation and relation to hepatic encephalopathy

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Abstract

Background: Liver transplantation (LT) helped to save the life of end stage liver disease (ESLD) patients; however, there is a debate on the persistence of cognitive impairment. The study aimed to evaluate cognitive functions in patients with ESLD before and after liver transplantation and to assess its relation to hepatic encephalopathy (HE). Thirty recipients 47.6 ± 11 years undergone living donor liver transplantation at the transplantation center of both Ain Shams Center for Organ Transplant and Egypt air organ transplant unit were prospectively assessed by Trail Making Test, Wechsler Memory Scale–Revised, Benton Visual Retention—for the evaluation of cognitive functions before and 3 months after transplantation.

Results: The mean age of the patients was 47.6 ± 11 years, 17 males and 13 females. Eight out of 30 (26.7%) had past history of hepatic encephalopathy. The study reported significant improvement in the post-operative 3 months scores of Trail Making Test part (A), the digit span forward test, digit span backward test and the correct score difference of the Benton Visual Retention, as *p* value was (0.02), (0.01) (0.02), and (0.01) respectively, compared to the pre-operative scores. However, there was no difference in the scores of part (B), verbal association I, II, information subtest of WMS. Cognitive performance showed no significant difference between patients with or without history of HE.

Conclusions: Patients with ESLD have significant cognitive impairment that showed improvement after LT; HE did not correlate with cognitive function. Hence, transplantation has a favorable outcome on the cognitive impairment.

Keywords: Cognitive functions, Cognitive impairment, Liver transplantation, Hepatic encephalopathy, Recipient

Background

Cirrhosis is a result of continuous liver injury, inflammation, fibrosis, and necrosis. Alcoholism and chronic hepatitis B and C commonly cause cirrhosis where hepatitis C is the most damaging [1].

Cirrhosis usually represents with end-stage liver disease (ESLD) where liver function is greatly compromised. The diminished ability to produce protein and detoxify substances results in symptoms of portal hypertension including hepatic encephalopathy [2]. The building up of toxic compounds mainly ammonia in the brain, alter cerebral function and cause progressive deterioration in the neurological function [3].

With the worsening of liver function, the transition from compensated asymptomatic cirrhosis to decompensated cirrhosis occurs which happens at a rate of about 5 to 7% per year [4].

Decompensated disease has poorer quality of life with greatest impairment in social functioning, physical functioning, and pain domains [5].

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Hepatic encephalopathy (HE) is a prevalent complication of decompensated cirrhosis that is seen in 50–70% of patients [6]. It manifests as minimal HE (MHE) showing subtle subclinical impairment of cognition only can be detected by neurophysiologic tests or as overt hepatic encephalopathy (OHE) [2]. Various studies showed that patients with either MHE or OHE had impaired health-related quality of life than patients without HE [7, 8].

Despite absence of any apparent clinical signs, minimal HE has been clearly shown to impact the quality of life of patient with chronic liver disease tremendously [9], as they had deficit in their attention, vigilance, memory, and orientation abilities [10]. The cognitive impairment also affects their ability to perform complex tasks such as driving, operation of machinery, and other work-related activities [11, 12]. MHE may also affect patient socio-economic status by interfering with work performance [13]. The presence of neurocognitive dysfunctions predicts not only development of overt hepatic encephalopathy but also premature death [14, 15].

Once decompensation has occurred the disease usually progresses more rapidly towards death or liver transplantation (LT) [16]. LT has long been the gold standard for the treatment of ESLD. It not only extends survival but also improves quality of life and psychological well-being of patients [17].

ESLD from viral hepatitis, together with alcoholic liver disease, is the main reason for liver transplantation in the USA [18]. In Egypt, hepatitis C-related ESLD is the main indication for liver transplantation and represents 89.8% of cases. Egypt harbors the highest prevalence rate of HCV infection in the world, estimated nationally at 14.7% [19].

In Egypt, cadaveric organ donation has been illegal; therefore, Egyptian patients with ESLD tend to seek cadaveric organ transplantation abroad. This led to the speedy in launching of living donor liver transplantation (LDLT) programs in Egypt [20]. It was first performed in Egypt in 1991. Currently, there are 13 LDLT centers in Egypt, including 6 university centers, 2 military centers, 3 private centers, and 2 centers in the ministry of health hospitals. In June 2014, the total number of cases reached 2406. This number comprised 2246 adult cases (93%) and 160 pediatric cases (7%) [21].

HE is presumed to be substantially reversed after successful LT [22]. Despite, it has been reported that there is a significant improvement in cognitive performance and health-related quality of life at 6 months post-LT, accompanied by a significant improvement in white matter integrity [23]. Some studies have reported the contrary [24]. That is why neuropsychological testing , may help during pre-transplant evaluation, as one of the inclusion assessment methods and furthermore it may help in the process of counseling and further prediction of post-transplant recipients level of function.

The current study aimed to evaluate cognitive functions in patients with end stage liver diseases before and after Liver donor liver transplantation and explore the effect of prior history of HE on cognitive function post-operatively.

Methods

Patients were selected from clients of the liver transplant unit from two centers: Ain Shams Center for Organ Transplant (ASCOT) in Ain Shams specialized hospital (usually operate 30 patients/year for transplant with average 3–5 drop out) and Egypt air organ transplant unit in Egypt Air Hospital in Almaza (20 patients/year undergo transplant with average 2–4 drop out) between the dates of March 2017 and April 2018 with the following inclusion and exclusion criteria.

Inclusion criteria includes (1) end stage liver disease, candidate for transplantation; (2) age from 18 to 60; (3) both gender; and (4) signed an informed consent to participate in the research. They were excluded if they were having unclear sensorium or delirious at time of assessment, having a major central neurological disease, severe renal, and pulmonary disease interfering with their abilities to withstand the assessment.

Because of the small number of clients who pass through both centres each year and only who signed consent was enrolled, a convenient sample of all patients was chosen for inclusion in the study with size 40 participant calculated using EpiInfo® version 6.0, setting the type-1 error (α) at 0.05 and the power (1-ß) at 0.80. The resulted sample size was 30 persons over the year course of the study with 10 drop out cases.

Design

It was a prospective comparative study. A pre-transplant assessment measures were compared to the post-transplant measures. The procedure of the study and the design were validated by the ethical committee of Ain Shams University, Cairo, Egypt.

In this study, the drop-out rate was 10 patients (they died within 1 week of the operation at the ICU due to severe medical or surgical complications). Comparison between patients group 30 and drop out 10 before liver transplantation revealed that; there was no statistical significance using the Fisher exact test between gender, age and medical past history in both groups of cases and the drop out as discussed previously in another paper [25].

Measures

Structured Clinical Interview for DSM-IV (SCID-I) [26]

The study used the Arabic version of the SCID-I [27] for exclusion of any psychiatric co-morbidity, full psychiatric and neurological examination to exclude delirium and any neurological disorders.

The Wechsler Memory Scale–Revised (WMS) [28]

It includes information and orientation questions, eight short term memory tasks and four delayed recall trials, all of which take about 45 min to 1 h to administer. In the current study, we used the following subtests: information and orientation to, digit span backwards and forwards, verbal paired association I, and verbal paired association II. The study used the Arabic version of WMS [29].

Benton Visual Retention Test [30]

It measures visual perception and visual memory. The individual examined is shown 10 designs, one at a time, and asked to reproduce each one as exactly as possible on plain paper from memory.

Trail Making Test (TMT) parts A and B [31]

This is a measure for task shifting ability and attention. In part A, the circles are numbered 1–25, and the patient should draw lines to connect the numbers in ascending order. In part B, the circles include both numbers (1–13) and letters (A–L); with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C). Scoring: results for both TMT A and B are reported in seconds; Trail A (average 29 s, deficient > 78 s) trail B (average 75 s, deficient > 273 s).

All tests were done 3–5 days before the liver transplant operation after the patient was admitted at the hospital. Then, they all were repeated 3 months after transplantation during their medical follow up at the hospital outpatient clinic.

Procedure

Between March 2017 and April 2018, each person admitted to both centers and who met the study inclusion criteria was immediately enrolled.

For those selected, the purpose of the study was explained, including the nature of the scales. Participants were assured confidentiality and were given an opportunity to decline to participate in the study. At intake, each selected recipient was subjected to SCID-I to exclude co-morbidity psychiatric and to neurological examination. Then, they underwent the following tests; the Trail Making Test part A and B, Wechsler Memory Scale–Revised (WMS-R), Benton Visual Retention.

In addition, measuring the severity of chronic liver disease using Child–Pugh score [32] and the MELD [33] score assessed by the tropical medicine physician.

– Three months post-transplant, Trail Making Test parts A and B, Wechsler Memory Scale–Revised (WMS-R), Benton Visual Retention Test were repeated.

Statistical analysis

The collected data was revised, coded, tabulated, and introduced to a PC using v19.0 IBM statistical package for social sciences and Microsoft Office 2010. Data was presented and suitable analysis was done according to the type of data obtained for each parameter. The significance level was identified at < 0.05 and marked by S, highly statistical significance at < 0.01 and marked by HS while non-significance was considered at $p > 0.05$ marked by NS.

Results

Thirty (17 males and 13 females) recipients who fulfilled the inclusion criteria were finally included in the study. Mean age was 47.6 ± 11 years. The majority had no medical comorbidity (56.7%). In terms of liver severity, MELOD's score mean was 16.60 ± 3.97 and 19 (63.3%) classified as Child–Pugh C denoting sever derangements in their liver functions and urgent need for transplantation. Eight (26.7%) had evidence of past history of hepatic encephalopathy.

Cognitive functions of the studied group before transplantation

The scores of each cognitive test was classified to presence of cognitive impairment as (yes) or absence of cognitive impairment as (no) compared to normal range or mean score of each test in standard population. As illustrated in Table 1.

Part A of Trail Making Test indicated that less than half of the sample 46.67% had problems in their focused attention; however, in part *B* of the test, it showed more than half of the patients 63.33% had good performance indicating that their executive functioning including processes of task-set inhibition, cognitive flexibility, and the ability to maintain a response set is not affected.

Regarding Wechsler Memory Scale, the general *information* knowledge and orientation in 86.67% patients had no impairment. *Verbal association subtest part 1* showed 70% of patients had problems in their immediate recall

Table 1 Comparison of cognitive functions before and after liver transplantation among recipients

	Before		Total	McNemar test	
	No	Yes		*p* value	Sig.
Trail making B					
After					
No	17 (56.67%)	2 (6.67%)	19 (63.33%)	1	NS
Yes	2 (6.67%)	9 (30%)	11 (36.67%)		
Total	19 (63.33%)	11 (36.67%)	30 (100%)		
Trail Making A					
After					
No	16 (53.33%)	7 (23.33%)	23 (76.67%)	0.02	S
Yes	0 (0%)	7 (23.33%)	7 (23.33%)		
Total	16 (53.33%)	14 (46.67%)	30 (100%)		
Information/orientation test of WMS					
After					
No	26 (86.67%)	4 (13.33%)	30 (100%)	0.13	NS
Total	26 (86.67%)	4 (13.33%)	30 (100%)		
Verbal association test part 1 of WMS					
After					
No	5 (16.67%)	7 (23.33%)	12 (40%)	0.55	NS
Yes	4 (13.33%)	14 (46.67%)	18 (60%)		
Total	9 (30%)	21 (70%)	30 (100%)		
Verbal association test part 2 of WMS					
After					
No	20 (66.67%)	5 (16.67%)	25 (83.33%)	0.06	NS
Yes	0 (0%)	5 (16.67%)	5 (16.67%)		
Total	20 (66.67%)	10 (33.33%)	30 (100%)		
Digit span forward test of WMS					
After					
No	19 (63.33%)	8 (26.67%)	27 (90%)	0.01	S
Yes	0 (0%)	3 (10%)	3 (10%)		
Total	19 (63.33%)	11 (36.67%)	30 (100%)		
Digit span backward test of WMS					
After					
No	7 (23.33%)	9 (30%)	16 (53.33%)	0.02	S
Yes	1 (3.33%)	13 (43.33%)	14 (46.67%)		
Total	8 (26.67%)	22 (73.33%)	30 (100%)		
Benton visual retention test correct score difference					
After					
No	13 (43.33%)	11 (36.67%)	24 (80%)	0.01	S
Yes	1 (3.33%)	5 (16.67%)	6 (20%)		
Total	14 (46.67%)	16 (53.33%)	30 (100%)		
Benton visual retention test error score difference					
After					
No	5 (16.67%)	7 (23.33%)	12 (40%)	0.18	NS
Yes	2 (6.67%)	16 (53.33%)	18 (60%)		
Total	7 (23.33%)	23 (76.67%)	30 (100%)		

memory while in *part 2* the majority of cases 20 (66.67%) had intact delayed recall memory.

Regarding attention and working memory, *digit span forward* subtest showed no impairment in 63% of patients while using *digit span backwards*, large number of patients 22 out of 30 (73.33%) showed impairment in test performance signifying more problems in their working memory.

Moving to their visual perception and visual memory assessed by the Benton Visual Retention Test

The difference between obtained and correct score showed that 16 patients were unable to reproduce the design matches to the original. Meanwhile, the *difference between obtained and expected error* score showed that 23 (76.67%) had high number of errors hence they had impaired visual memory abilities.

Comparison between cases before and after liver transplantation regarding cognitive functions

We compared the scores of each cognitive test using the McNemar test, before and after liver transplantation regarding the presence (yes) and absence of cognitive impairment (no). The findings were demonstrated in Table 1 as follows.

Recipients showed significant improvement in Trail Making Test part (A) after liver transplantation ($P=0.02$), where 14 patients before surgery had impaired test performance and after surgery only 7 patients had impaired performance as surgery enhanced their attention ability.

In spite that there was no statistically significant difference regarding information subtest of WMS ($p=0.13$), verbal association test part 1 ($p=0.55$) and 2 ($p=0.06$), pointing no improvement in memory, immediate and delayed recall. Yet, the digit span forward test shows significant improvement after liver transplantation ($P=0.01$), as 11 patients had impaired test performance before surgery and turned to be only 3 after surgery which means improvement in their attention efficiency and capacity. Similarly, same improvement was noticed in the digit span backward test ($P=0.02$), where the number of patients showing impairment, declined from 22 to 14 patients after surgery denoting better working memory ability.

Also, significant improvement was found in the correct score difference of the Benton visual retention test after liver transplantation ($P=0.01$), where 16 patients before surgery had impairment in test performance decreased to only 6 patients after surgery; hence, their visual perception and visual memory improvement.

Table 2 Comparison between patients had past history of HE and those who did not have past history of HE regarding the change in the state of cognitive function tests

Change	Past H.E				Fisher exact test	
	Yes		No			
	N	%	*N*	%	*p* value	sig.
Trail Making B						
The same	6	75.0%	20	90.9%	0.284	NS
Improved	1	12.5%	1	4.5%		
Became impaired	1	12.5%	1	4.5%		
Trail Making A						
The same	6	75.0%	17	77.3%	1.000	NS
Improved	2	25.0%	5	22.7%		
Inform/orientation						
The same	6	75.0%	20	90.9%	0.284	NS
Improved	2	25.0%	2	9.1%		
verb.PA1						
The same	6	75.0%	13	59.1%	0.703	NS
Improved	2	25.0%	5	22.7%		
Became impaired	0	0.0%	4	18.2%		
Verb.PA2						
The same	6	75.0%	19	86.4%	0.589	NS
Improved	2	25.0%	3	13.6%		
Became impaired	0	0.0%	0	0.0%		
DS forward						
The same	6	75.0%	16	72.7%	1.000	NS
Improved	2	25.0%	6	27.3%		
DS backward						
The same	5	62.5%	15	68.2%	0.316	NS
Improved	2	25.0%	7	31.8%		
Became impaired	1	12.5%	0	0.0%		
BVRT DIFF C						
The same	6	75.0%	12	54.5%	0.758	NS
Improved	2	25.0%	9	40.9%		
Became impaired	0	0.0%	1	4.5%		
BVRT DIFF E						
The same	6	75.0%	15	68.2%	1.000	NS
Improved	2	25.0%	5	22.7%		
Became impaired	0	0.0%	2	9.1%		

Verb.PA1 Verbal association part 1, *Verb.PA2* Verbal association part 2, *BVRT Diff C* Benton Visual Retention Test in corrected score difference, *BVRT Diff E* Benton Visual Retention Test in error score difference, *DS forward* Digit span forward, *DS backward* Digit span backward

Correlation between history of hepatic encephalopathy and scores of cognitive function tests after liver transplant

We chose hepatic encephalopathy as a variable to test cognitive functions as this is the main problem affecting cognitive function and experienced by most of end stage liver disease patients.

Table 2 shows no statistically significant results using the Fisher exact test, comparing between those who had past history of HE (yes) and those who did not have past history of HE (no) regarding the change in the state of cognitive function tests (improved, became impaired, and the same) before and after liver

transplantation. However, some findings show large difference in number but still statistically not significant.

Discussion

Liver transplantation remains the only way to cure patients with ESLD. Important questions about cognitive sequelae and its impact on quality of life after LT have emerged. Determination of the impact of LDLT on cognitive functions is considered an outcome measure of transplantation, as it aims to improve the recipient's well-being. In this study, we discussed the cognitive changes associated with LDLT in relation to HE.

The study included 30 cases, 17 of which were male and 13 females, the mean age of recipients was 47.6 ± 11. They were assessed 3 days before the transplantation surgery and 3 months post-transplant.

Previous studies showed that patients with liver cirrhosis with minimal hepatic encephalopathy exhibited poor performance on neuropsychological examinations when compared with normal control subjects [34, 35]. It has been estimated that 1.5–2 million people may have cognitive impairment associated with liver disease in North America [36]. In this study, neuropsychological tests before liver transplantation showed impairment in several domains. Where recipients performed poorly in the domains of memory, attention, and psychomotor speed, but there was no affection in the performances on the information/orientation subtests and delayed recall memory in most of the patients.

As 70% of the patients had problems in their immediate recall memory and 76.67% showed impairment in their visual memory abilities. Also, 73.33% demonstrated deficits in their working memory. This finding is in agreement with the findings of Bahceci et al. [37] where they reported 36–92% decrement in various memory scores in cirrhotic patients when compared to healthy controls.

Conforming with different studies reporting that attention and concentration were frequently impaired in cirrhotic patients without overt hepatic encephalopathy [38, 39]. The present study found 46.67% of participants scored lower on the attention/concentration scales. In contrast to another study which showed normal attention abilities in patients with liver cirrhosis without overt hepatic encephalopathy [40].

This could be explained by previous reports stating that patients with more severe disease (Child–Pugh Stage C) display greater cognitive deficits than patients with less severe disease on tests of immediate memory, processing speed and attention tasks [34, 38] and 63.3% of our patients classified as Child–Pugh Stage C. The cognitive abnormalities possibly result from pathogenic processes such as those occurring in overt HE related to the entry of ammonia into the brain tissue via the arterial circulation [41].

Despite the findings in a study noting impairment of orientation tasks in patients with minimal hepatic encephalopathy [37]. In the current study, most of patients 86.67% had no impairment in the orientation scores which was in accordance with Adekanle et al.'s [42] study as they did not report difference in orientation scores between the patients with liver cirrhosis and normal control subjects and they justify their finding by the small sample size and the difference in cognitive tools employed which could be similar valid reason in the current study.

On comparing the cognitive tests of the present study participants three months after undergoing liver transplantation with values obtained before LT. Recipients showed significant improvement in Trail Making Test part A ($P=0.02$) in 23.33%, indicating that the surgery enhanced their psychomotor speed and attention ability while no significant improvement on part B. Similarly, other authors have observed differences between orthotopic liver transplantation (OLT) patients and control subjects on part A, but not on part B [43–45]. Contrary [46–48] studies found significant improvement in both Trail Making Test part A and B post-transplantation. This could be due to the lower age of our patients compared to those studies and pre-operatively most of our patients 63.33% showed normal task on trial B.

On the Digits Forward and Digits Backward tests of WMS, recipient post-transplant achieved higher scores than pre-transplant, reflecting a recovery of their attention capacity and short-term memory. This improved performance in digit span tests had already been described by Oppong et al. [49] in patients assessed pre- and post-liver transplantation and also Pantiga et al. [34] reported that OLT group showed better scores than cirrhotic patients group.

The results obtained by the Benton Visual Retention Test showed improvement in the correct score difference indicating more ability to reproduce the design matches the original pictures correctly, which is a reflection of improvement in visual perception and visual memory. In line with [45, 50] showing same improvement in visual perceptive following liver transplantation. Also, [34] reported that OLT had better results on visuo-perceptive skills than patients with liver cirrhosis.

The changes in the cognitive functions observed in recipient post-transplant can be explained by the changes in the amount of brain edema. Where the hyperammonemia occurring during liver failure which induced an increase in blood–brain barrier permeability [51], leading to mild diffuse brain oedema with associated increased brain glutamine, causing astrocytic swelling

[52] and injury to axons, myelin, and glial cells which consequently can lead to neuropsychological decline, that became reversible after transplantation [53]. As the volume of these changes decrease with liver transplantation explaining the improvement shown in the neuropsychological function [45].

On the other hand, the results of the information subtest of WMS, verbal association test parts 1 and 2, showed no significant improvement following transplantation. This lack of recovery in LDLT recipients could be related to the viewpoint that the manifestations of HE are not completely fully reversible by transplantation [54]. As, HE not only cause metabolic dysfunctions, but also characterized by changes in cerebral morphology that would explain why these patients do not make a full recovery [55].

In the current study we divided the sample into 2 groups: those who experienced Hepatic encephalopathy (8 patients) and those who did not have any history of hepatic encephalopathy (22 patients), and then we compared between both groups as regards cognitive functions state before and after liver transplantation.

The present study showed no statistically significant difference in any of cognitive functions tests state before and after liver transplantation regarding presence and absence of previous episode of HE. Similarly, Sotil et al. [24] who tested the influence of overt HE on post-operative neurocognitive function by comparing patients who had suffered from overt HE prior to their procedure (HE-PreLT group) to that of a similar group of patients ($n=14$) without overt HE (No HE-PreLT group), the Repeatable Battery for the Assessment of Neuropsychological Status testing did not show differences between the 2 groups. Also, Cheng Y and his colleagues [56] found no significant differences between HE and no HE, where both demonstrated poorer cognitive performance than Healthy Controls before LT. Yet, after transplantation patient with no HE showed better recovery after transplantation compared to the HE group.

Inconsistent to the current study Campagna and colleagues [48] and Bajaj J and colleagues [57] stated that patients with a history of OHE showed worse cognitive performance before LT and greater cognitive improvement after LT in comparison with their counterparts with a negative history. Also, Garcia-Martinez et al. [54] study that found that susceptibility to persistent cognitive deficits is higher among patients with prior episodes of HE.

The results of the current study demonstrating the presence of past history of HE showed no difference in neurocognitive function pre- and post-LT could be explained by 4 factors. First, the cohort studied is relatively small as 8 out of 30 had history of HE. Second, it is possible that the no HE group could have suffered from minimal HE at the time of the procedure, which is secondary to liver failure and shares the same pathogenic mechanism as overt HE however could not be detected clinically [58]. Third, cognitive impairment could be due to the impact of another factors rather than hepatic encephalopathy as systemic inflammation caused by cirrhosis which tend to demonstrate long-lasting cognitive impairment after infection. Other causes are the changes in cerebral blood flow and systemic hemodynamics [59]. Finally, we studied patients at a single point in time with shorter follow-up duration 3 months after LT. Some longitudinal studies have noted a progressive improvement in neurocognitive function during the first year after OLT [60].

Conclusions

This study has shown that patients with ESLD performed poorly in the domains of short-term memory, attention, visual perception and visual memory yet fair well on orientation and executive functions. Following LDLT their attention, short memory and visual memory improved. However, the hepatic encephalopathy did not correlate with cognitive functions of the recipients. Detecting these cognitive alterations is of considerable interest and importance because of the impact they have on the daily lives of these patients and because of the need to inform the patients about the impact of liver transplantation procedure on their cognitive functions to take it in consideration in their decision process.

Limitation

The current study was the first Egyptian study concerned with the effect of liver transplantation on cognitive function of patients. The study chooses prospective design with a lot of valid and reliable tools to assess cognitive function. However, it is limited by a small sample size related to the strict duration and the drop out from increased mortality in the patients post-transplant. And the short duration of following up for the recipient, so recommending future studies to use longer duration that might prove more improvement in cognitive functions.

Abbreviations

LT: Liver transplantation; ESLD: End stage liver disease; HE: Hepatic encephalopathy; MHE: Minimal hepatic encephalopathy; OHE: Overt hepatic encephalopathy; LDLT: Living donor liver transplantation; WMS: Wechsler Memory Scale.

Acknowledgements

Not applicable.

Authors' contributions
All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AA, GM, DM, and RH. AM and MA reviewed the whole study findings. The first draft of the manuscript was written by RH. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The procedure of the study and the design were accepted and validated by the ethical committee of Ain Shams University, Cairo, Egypt. Informed consent was given by the participants.

Consent for publication
The participants gave consent for using their data in publication.

Competing interests
The authors declare that they have no competing interests.

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Received: 16 December 2021 Accepted: 3 January 2022
Published online: 14 January 2022

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