

Minimal Hepatic Encephalopathy

Longitudinal Effects of Liver Transplantation

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Background: The long-term effects of liver transplantation (LT) on minimal hepatic encephalopathy are poorly documented.

Objective: To assess the cognitive performance of patients with cirrhosis and without overt encephalopathy, before and after LT.

Design: Longitudinal study comparing cognitive performance of patients with cirrhosis before LT and 6 to 18 months after LT, with matched control patients.

Setting: University medical center.

Results: Six months after LT, patients had improved their performance in visuospatial and selective attention, vi-

suospatial short-term and long-term memory, and language tasks. After 18 months, a further improvement was found for selective attention and verbal short-term memory, while no other cognitive functions varied over time.

Conclusions: The present findings confirm preliminary studies showing that LT improves cognitive functions in patients with cirrhosis. The cognitive improvement is not generalized, but appears prominent in attention and memory and, once achieved, remains stable. Rates of recovery differ, being early for some functions and later for others.

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A WIDE RANGE OF NEUROPSYCHIATRIC abnormalities, such as personality disorders, inappropriate affective, behavioral, and sleep disturbances, and cognitive and psychomotor impairment, can occur in patients with liver cirrhosis,¹ usually classified as *hepatic encephalopathy* (HE). Conventionally, HE is graded according to 4 stages of severity on the basis of clinical examination,¹ but the absence of clinical signs does not exclude the diagnosis of HE.^{2,3} In patients without overt neuropsychiatric symptoms, cognitive deficits can be detected by neuropsychological tests⁴ disclosing subclinical or minimal HE (MHE). Minimal hepatic encephalopathy is often associated with patient complaints about reduced work efficiency⁵ and probably predisposes to overt HE.⁶

The profile of cognitive dysfunctions associated with MHE is still under study. Selective deficits in attention and fine motor skills have been observed, with spared general intellectual abilities.^{4,7} This pattern of cognitive deficits suggests subcor-

tical cerebral impairment. Recent neuroimaging studies using positron emission tomography,^{8,9} magnetic resonance imaging,¹⁰ or magnetic resonance spectroscopy^{11,12} confirm the prominent involvement of frontosubcortical structures.

The most recent innovative and radical treatment of liver disease is liver transplantation (LT). The surgical outcomes and extension of life following LT have been validated, but the effects of LT on MHE are poorly known. Few studies¹³⁻¹⁵ have systematically compared the cognitive performance of patients with cirrhosis before and after LT; they demonstrated some cognitive improvement, with substantial individual differences. However, these observations were made in small cohorts (fewer patients than the number transplanted, implying an attrition effect), often with liver diseases of different etiology, and patients probably had a practice effect on some tests. In addition, scant information was given on long-term effects regarding the range of improvements and their duration and stability.

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We designed a longitudinal study comparing the cognitive performance of a group of patients with cirrhosis of viral and biliary etiology before LT and 6 to 18 months after LT, with matched control patients.

METHODS

SUBJECTS

Patients with liver cirrhosis were enrolled from January 20, 1998, to November 25, 1999, among those seen consecutively for a neurological assessment before inclusion on the waiting list for LT, according to the general LT protocol. The study ended on October 29, 2002.

Exclusion criteria were age younger than 20 years and older than 60 years, educational level less than 3 years, overt HE at any time during the study, neurological and psychiatric diseases, addiction to psychotropic drugs, alcohol abuse, history of vascular cerebral disease, and severe intellectual impairment as detected by a score of less than 18.9 on the Raven Coloured Progressive Matrices.¹⁶

Seventy-eight patients met the criteria and underwent psychometric assessment as candidates for inclusion in the sample. A control group of 23 patients (**Table 1**) seen at the gastroenterology day clinic for illness that did not interfere with mental functions was also examined. The exclusion criteria were the same as those used for the patients with cirrhosis.

The study was approved by the institutional review board of the LT committee of our hospital, in accord with principles enumerated in the Declaration of Helsinki in 1998. Patients gave their informed consent to participate in the study.

NEUROPSYCHOLOGICAL ASSESSMENT

Tests were planned for each patient before LT (T0) and 6 months (T1) and 18 months (T2) after LT. Whenever possible, the control group was examined twice, the second assessment being performed about 400 days after the first.

Psychometric tests were chosen to allow detection and measurement of specific cognitive deficits associated with MHE. Tests were clustered as follows:

Attention

Visuospatial attention was examined by Visual Matrices,¹⁸ Cross Out a Test, and Trail-Making Test (TMT) A and B¹⁹; selective attention was assessed by the Stroop color test.²⁰ Sustained attention was evaluated by auditory reaction time, visual reaction time, visual reaction accuracy, and visual accuracy test.

The measures of the Stroop color test, TMT, Cross Out a Test, auditory reaction time, visual reaction time, and visual accuracy test are computed on a reversed scale, in which low values indicate the best function; in the other tests, a high value is a sign of good functioning.

Memory

Verbal short-term memory was examined by Digit-Span,²¹ and visuospatial short-term memory was evaluated by the Corsi test¹⁸ and immediate visual memory test.¹⁶ Verbal learning was assessed by the Rey Auditory Verbal Learning Test, immediate and 15-minute delay recall,¹⁶ brief story,¹⁸ and paired-associate learning²²; visuospatial learning was assessed by the Rey-Osterrieth Complex Figure Recall Trial²³ and supraspan learning.¹⁸

Language was examined by word fluency¹⁶ and the phrase construction test.¹⁶ Visuospatial constructional skills were ex-

Table 1. Demographic and Clinical Data of Samples*

Characteristic	Patients With Cirrhosis (n = 23)	Control Subjects (n = 23)
Age, y	46.52 ± 7.45	46.95 ± 7.06
Male/female, No.	18/5	18/5
Educational level, y	9.17 ± 3.15	9.17 ± 3.24
Child-Pugh ¹⁷ class	9.50 ± 1.90	...
Cirrhosis etiology, No.		...
Viral	21	
Biliary	2	

*Data are given as mean ± SD unless otherwise indicated.

amined by the Rey-Osterreith Complex Figure and Painting Copy tests.¹⁶ Motor speed was assessed with the Digit Symbol Substitution Test,²⁴ and spatial planning intelligence was assessed with the Elithorn maze test.¹⁸

All tests are well-validated psychometric instruments. When needed, scores were corrected for age, sex, and educational level. The psychometric screening was performed for each patient on the same day as the neurological examination.

The final analysis, to compare psychometric performance before LT and 6 months after LT, was conducted in 23 patients (Table 1). Several factors reduced the initial number of 78 patients screened (**Figure**). Therefore, all 3 neuropsychological assessments were only obtained in 13 patients. Two patients died before LT because of liver function deterioration. Rejection or primary nonfunction was the cause of death after surgery in 10 patients or the reason for retransplantation in 4 patients. Patients who moved to other medical centers did so for geographical convenience.

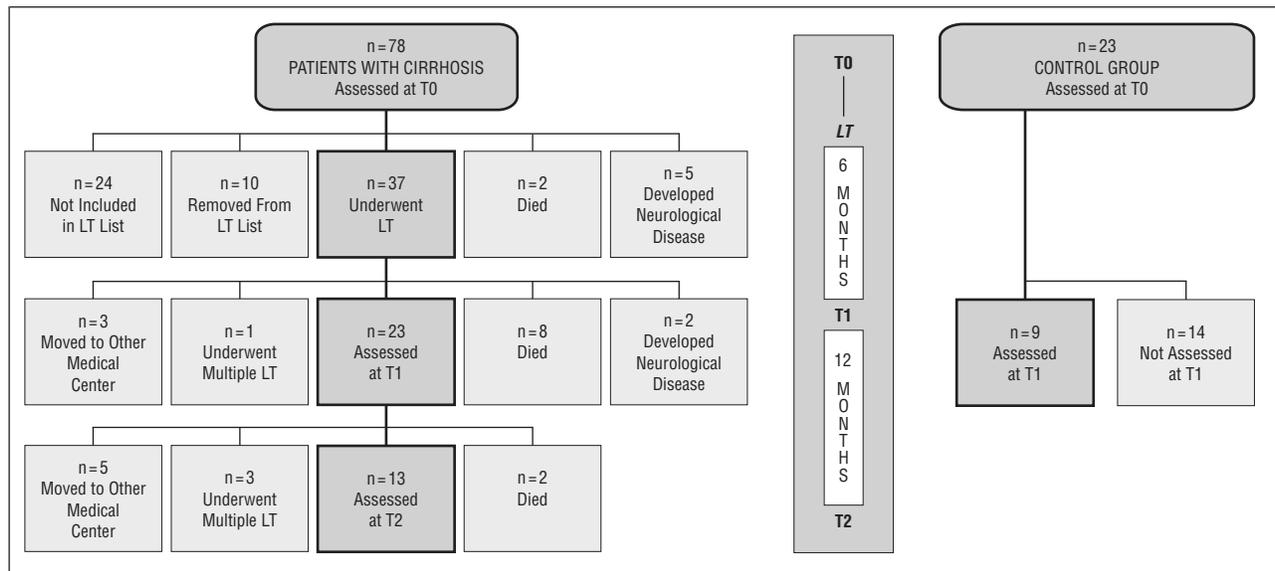
Patients awaiting a liver transplant underwent surgery on average 174 days (range, 24-494 days) after the first assessment. Immunosuppression therapy consisted of cyclosporine use in 14 patients and tacrolimus (FK506) use in 9 patients.

STATISTICAL ANALYSIS

Because of the large number of neuropsychological variables and the different sample sizes in the 3 follow-up tests, we analyzed data by means of separate blocks of analyses: 8 multivariate analyses of variance (ANOVA) for cognitive functions represented by several tasks assumed to be cognitively homogeneous and 3 univariate ANOVA for cognitive functions represented by one single task. Each group of analyses was repeated for each step. When needed, several multiple comparisons and post hoc analyses with Bonferroni correction were conducted.

First, to check for a possible attrition effect due to a substantial reduction in the sample, we compared the performance of 23 patients who underwent transplantation at T0 with that of 49 patients who were unavailable for follow-up, excluding patients who died, developed HE before LT, or developed neurological problems after surgery. The 2 groups differed significantly in age (mean, 51.9 vs 46.5 years), so this factor was used as a covariate in the analyses. For the same reason, we compared the T1 performance of the patients who completed all measures scheduled (13 patients) with that of the patients without a third evaluation (10 patients). We conducted the same analyses to check for an attrition effect on T0 cognitive performance in the control group (23 control patients who completed 2 measures vs 14 control patients without a second evaluation).

Second, we compared T0 cognitive performance between 23 patients and 23 matched control patients. Third, to examine several possible differences in 13 patients' performance be-



Basic design and subjects' progress through the study. LT indicates liver transplantation; T0, before LT; T1, 6 months after LT; and T2, 18 months after LT.

fore LT and 6 months and 18 months after LT, we compared patients' cognitive indicators at T0, T1, and T2. In addition, to reinforce the results of the comparison between T0 and T1, data from a larger sample (23 patients) that had only 2 measures were analyzed. The fourth step was to compare patients and controls in the second evaluation (T1). Fifth, to disclose a possible practice effect, we conducted the same sequence of analyses on the control group to compare T0 and T1 performance.

Statistical analysis was performed using the software package SPSS 9.0 for Windows.²⁵

RESULTS

Preliminary ANOVA to check for an attrition effect did not suggest statistical differences in cognitive functions in the groups compared. A sequence of multivariate ANOVA showed significant differences between patients before LT and control patients in the following: visuospatial attention ($F_{4,40}=5.32, P<.01$), selective attention ($F_{1,43}=7.47, P<.01$), sustained attention ($F_{4,40}=4.12, P<.01$), and visuospatial short-term memory ($F_{2,43}=7.43, P<.01$). Separate ANOVA on each measure suggested differences in the following: Visual Matrices ($F_{1,43}=15.32, P<.01$), TMT A ($F_{1,43}=15.60, P<.01$), TMT B ($F_{1,43}=9.63, P<.01$), Stroop color test time ($F_{1,44}=11.09, P<.01$), Stroop color test errors ($F_{1,44}=8.70, P<.01$), visual accuracy test ($F_{1,43}=17.33, P<.01$), visual reaction time ($F_{1,43}=4.38, P<.05$), Corsi test ($F_{1,44}=7.29, P<.05$), immediate visual memory test ($F_{1,44}=10.76, P<.01$), memory span ($F_{1,44}=22.47, P<.01$), Digit Symbol Substitution Test ($F_{1,44}=34.82, P<.01$), and Elithorn maze test ($F_{1,44}=23.62, P<.01$). **Table 2** gives results of the post hoc range test.

Multivariate ANOVA comparing 13 patients' performance before LT and 6 and 18 months after LT suggested an overall improvement in performance with time on the following: selective attention ($F_{4,9}=9.35, P<.01$), sustained attention ($F_{8,5}=6.41, P<.05$), visuospatial short-term memory ($F_{4,9}=6.04, P<.05$), and language ($F_{4,9}=10.26, P<.01$). Separate ANOVA on each measure suggested improvement on the following: Stroop color test

reaction time ($F_{2,24}=11.35, P<.01$), word fluency ($F_{2,24}=3.76, P<.05$), and phrase construction test ($F_{2,24}=5.11, P<.01$). Improvement over time was also found on the Digit Symbol Substitution Test ($F_{2,11}=16.46, P<.01$) and memory span ($F_{2,11}=5.51, P<.06$). In sustained attention and visuospatial short-term memory, no single comparison reached statistical significance (**Table 3**).

Multivariate ANOVA comparing 23 patients' performance before LT and 6 months after LT detected a significant improvement with time on the following: visuospatial attention ($F_{4,19}=4.39, P<.05$), selective attention ($F_{2,21}=4.77, P<.05$), visuospatial learning ($F_{2,21}=5.32, P<.05$), and language ($F_{2,20}=5.96, P<.01$). Separate ANOVA suggested improvement on the following: Visual Matrices ($F_{1,22}=12.70, P<.01$), TMT B ($F_{1,22}=6.83, P<.05$), Stroop color test time ($F_{1,22}=5.57, P<.05$), Stroop color test errors ($F_{1,22}=5.76, P<.05$), Rey-Osterrieth Complex Figure Recall Trial ($F_{1,22}=8.97, P<.01$), and phrase construction test ($F_{1,21}=12.39, P<.01$). Analysis of variance suggested a similar significant effect on the Digit Symbol Substitution Test ($F_{1,22}=28.53, P<.01$) and Elithorn maze test ($F_{1,22}=18.13, P<.01$).

No differences were found between patients and controls at T2, except for on memory span ($F_{1,29}=4.08, P<.05$). Analyses conducted between T0 and T1 performance in the control group suggested no significant differences in any cluster of cognitive functions.

COMMENT

This is the first study to investigate the long-term effects of LT on MHE in a large sample of patients with homogeneous types of chronic liver disease. The control group was selected among patients without diseases interfering with normal cerebral functioning.

In keeping with reports in the literature, our sample, free from overt HE, exhibited reduced cognitive performance compared with control patients. We found specific differences on several attention components, ver-

Table 2. Neuropsychological Scores of 23 Patients and 23 Control Subjects at Baseline and Statistical Results*

Test	Patients (n = 23)	Control Subjects (n = 23)	P Value
Visuospatial attention			.002
Visual matrices	43.15 ± 6.46	50.30 ± 5.76	.001
Trail-Making Test A	45.60 ± 19.50	26.59 ± 11.62	.001
Trail-Making Test B	146.20 ± 97.94	78.31 ± 30.92	.003
Cross Out a Test	4.08 ± 5.90	1.72 ± 1.35	.07
Selective attention Stroop color test			.002
Time	43.43 ± 16.69	29.69 ± 10.62	.005
Errors	2.04 ± 2.72	0.30 ± 0.76	.002
Sustained attention			.007
Auditory reaction time	200.86 ± 40.19	184.46 ± 33.90	.15
Visual accuracy test	8.95 ± 8.49	1.27 ± 1.69	.001
Visual reaction time	411.32 ± 55.48	376.95 ± 54.68	.04
Visual reaction accuracy	2.43 ± 2.99	1.90 ± 1.34	.45
Verbal short-term memory span	4.72 ± 0.81	6.07 ± 1.10	.001
Visuospatial short-term memory			.002
Corsi test	4.53 ± 0.92	4.27 ± 0.99	.01
Immediate visual memory test	18.99 ± 2.93	21.13 ± 1.05	.002
Verbal learning			.36
Rey Auditory Verbal Learning Test			
Immediate	45.23 ± 8.34	49.30 ± 8.59	.10
15-Minute delay recall	10.19 ± 2.85	10.86 ± 2.53	.42
Brief story	10.37 ± 3.81	11.07 ± 3.20	.52
Paired-associate learning	14.29 ± 3.32	13.69 ± 3.37	.65
Visuospatial learning			.16
Supraspan learning	15.82 ± 4.24	18.06 ± 4.00	.07
Rey-Osterrieth Complex Figure Recall Trial	18.68 ± 5.66	20.08 ± 6.38	.44
Language			.39
Word fluency	31.90 ± 10.04	33.38 ± 11.05	.59
Phrase construction test	20.76 ± 2.65	22.30 ± 4.07	.17
Visuospatial constructional skill			.33
Painting Copy	11.23 ± 1.62	11.70 ± 0.67	.23
Painting Copy F	68.94 ± 1.69	69.62 ± 0.70	.08
Rey-Osterrieth Complex Figure	34.48 ± 1.93	35.07 ± 2.30	.40
Digit Symbol Substitution Test	29.56 ± 13.43	55.34 ± 16.08	.001
Elithorn maze test	12.20 ± 2.25	14.84 ± 1.40	.001

*Data are given as mean ± SD unless otherwise indicated.

bal and visuospatial short-term memory, and spatial planning and psychomotor speed, consistent with the presence of MHE. It is possible that the deficits concerning several domains of attention and short-term memory were related to each other, and this relationship probably characterized the course of recovery, but because of the study design, our data could not determine the direction of this relationship.

The neuropsychological assessment after LT indicated that visuospatial and selective attention improved during a short period, probably because these tasks were the most impaired before surgery. The results 6 months after LT are congruent with information provided by studies evaluating cognitive performance early after LT. Tarter et al¹³ suggested that 4 months after LT cognitive functions are restored to a large extent, but not completely, compared with a control group. Reither and colleagues¹⁴ found that cognitive performance approaches normal values by 1 year after LT, with most improvement occurring between 3 and 6 months after surgery. Moore et al¹⁵ reported improvement as early as 3 months after LT, which remained stable during subsequent testing.

After 6 months, we also observed an improvement in the spatial component of short-term and long-term

memory, in linguistic tasks that involve a frontal function such as lexical access, and in psychomotor speed. Selective attention continued to improve slightly, but significantly, until the 18-month assessment, while no other cognitive functions varied over time. Verbal short-term memory improved significantly only after 18 months.

Therefore, our data indicate that the improvement in cognitive performance after LT is not generalized to all cognitive functions and is stable once achieved. A further increase in some processes could occur in the long term.

This result does not seem to be an artifact of repeated-measures testing, because the control group performance remained unchanged over time, although this is inconclusive because of the absence of a third evaluation in the control patients. Compared with the control group, even at 6 months, performance differences disappeared, except for verbal short-term memory. Hence, the cognitive course seems globally directed toward a return to normality, although this recovery is slower for verbal short-term memory than for other cognitive functions.

To obtain a comprehensive estimate of HE reversibility, we conducted analyses to check for an attrition

Table 3. Neuropsychological Scores of 13 Patients Tested at All 3 Assessments and Statistical Results*

Tests	Patient Score			P Value Main Effect	P Value		
	T0	T1	T2		T0 vs T1	T0 vs T2	T1 vs T2
Visuospatial attention				.13			
Visual matrices	42.97 ± 7.29	49.44 ± 5.01	49.90 ± 5.35		.01	.04	>.99
Trail-Making Test A	45.84 ± 22.61	34.69 ± 12.08	35.07 ± 7.78		.08	.19	>.99
Trail-Making Test B	117.46 ± 57.55	91.23 ± 51.49	92.92 ± 43.32		.37	.38	>.99
Cross Out a Test	2.38 ± 2.36	2.00 ± 1.47	1.30 ± 1.49		>.99	.50	.44
Selective attention Stroop color test				.003			
Time	43.43 ± 16.69	36.56 ± 11.28	27.38 ± 9.11		.76	.001	.003
Errors	02.04 ± 02.72	0.95 ± 1.46	0.23 ± 0.59		.47	.09	.11
Sustained attention				.13			
Auditory reaction time	201.84 ± 48.18	195.60 ± 27.38	184.39 ± 33.29		>.99	.65	.02
Visual accuracy test	6.84 ± 5.65	5.69 ± 4.04	4.07 ± 3.17		>.99	.58	.52
Visual reaction time	403.65 ± 46.78	392.94 ± 38.29	377.31 ± 40.71		>.99	.18	.41
Visual reaction accuracy	2.38 ± 2.06	1.69 ± 1.31	1.61 ± 1.04		.82	.58	>.99
Verbal short-term memory span	4.80 ± 0.82	4.73 ± 1.03	5.61 ± 0.97	.02	>.99	.06	.01
Visuospatial short-term memory				.01			
Corsi test	4.48 ± 0.94	5.00 ± 1.12	5.28 ± 0.80		.35	.06	.73
Immediate visual memory test	20.62 ± 1.08	20.50 ± 1.75	21.43 ± 0.72		>.99	.07	.18
Verbal learning				.10			
Rey Auditory Verbal Learning Test							
Immediate	43.14 ± 8.56	45.20 ± 8.71	50.14 ± 9.12		>.99	.006	.07
15-Minute delay recall	9.45 ± 2.57	9.70 ± 2.59	11.15 ± 3.39		>.99	.04	.14
Brief story	9.63 ± 4.08	10.85 ± 3.53	11.79 ± 2.10		>.99	.32	.69
Paired-associate learning	14.25 ± 4.00	12.96 ± 3.65	14.50 ± 3.45		.51	>.99	.62
Visuospatial learning				.05			
Supraspan learning	15.96 ± 4.93	18.11 ± 3.78	19.01 ± 4.56		.31	.02	>.99
Rey-Osterrieth Complex Figure Recall Trial	19.23 ± 6.76	23.47 ± 7.06	23.29 ± 5.24		.12	.07	>.99
Language				.002			
Word fluency	32.18 ± 11.53	34.93 ± 10.99	35.72 ± 10.60		.15	.06	>.99
Phrase construction test	20.82 ± 1.88	22.92 ± 1.98	23.26 ± 3.58		.008	.10	>.99
Visuospatial constructional skill				.67			
Painting Copy	11.59 ± 0.89	11.74 ± 0.56	11.90 ± 0.30		>.99	.93	>.99
Painting Copy F	68.87 ± 1.95	63.30 ± 0.76	69.75 ± 0.56		>.99	.32	.23
Rey-Osterrieth Complex Figure	34.49 ± 1.90	33.88 ± 2.58	34.55 ± 1.54		>.99	>.99	>.99
Digit Symbol Substitution Test	31.61 ± 14.09	47.23 ± 11.42	48.46 ± 15.09	.001	.001	.001	>.99
Elithorn maze test	12.34 ± 2.61	13.92 ± 1.44	14.26 ± 1.50	.12	.14	.13	>.99

Abbreviations: T0, before transplantation; T1, 6 months after T0; T2, 18 months after T0.
*Data are given as mean ± SD unless otherwise indicated.

effect, to eliminate selection bias as much as possible. The differences between the assessments before and after LT indicate improvement in cognitive functions, as the sample analyzed approximated the patient population as a whole.

Our neuropsychological findings are also in keeping with results of the few neuroimaging studies of patients with cirrhosis before and after LT. Positron emission tomography results obtained by Burra et al⁸ show an increased metabolic rate for glucose after LT in the cingulate, frontal regions, and hippocampus, areas critical for memory and attention.^{26,27} On magnetic resonance imaging, basal ganglia abnormalities seen in patients with cirrhosis decrease after LT, but are still evident after 6 months,²⁸ indicating that the restitution of normal signal intensity in the basal ganglia could be a slow and continuous process. This is supported by our finding of a progressive ongoing recovery of some functions such as memory span and selective attention.

In conclusion, LT has a favorable effect on MHE, which continues during longitudinal observation. Fur-

ther prospective and longitudinal studies will target specific structural or biochemical changes in patients who have received a transplant.

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