Lactulose Improves Cognitive Functions and Health-Related Quality of Life in Patients with Cirrhosis Who Have Minimal Hepatic Encephalopathy

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Minimal hepatic encephalopathy (MHE) has a negative effect on patients' daily functioning. Thus far, no study has investigated the effect of treatment-related improvement in cognitive functions on health-related quality of life (HRQOL). We measured psychometric performance by number and figure connection tests parts A and B, picture completion, and block design tests and HRQOL by the Sickness Impact Profile (SIP) of 90 patients with cirrhosis on inclusion into the study and 3 months later. A *Z* score less than −2 on the neuropsychological (NP) tests was considered abnormal. Sixty-one (67.7%) patients had MHE. They were randomly assigned in a 1:1 ratio to receive treatment (lactulose) for 3 months (n = 31) or no treatment (n = 30) in a nonblinded design. The mean number of abnormal NP tests decreased significantly in patients in the treated group (baseline, 2.74 [95% CI 2.40-3.08]; after 3 months, .75 [95% CI .36-1.16]) compared with patients in the untreated group (baseline, 2.47 [95% CI 2.19-2.74]; after 3 months, 2.55 [95% CI 2.16-2.94]); multivariate analysis of variance (MANOVA) for time and treatment, *P* = 0.001. The mean total SIP score improved among patients in the treated group (baseline, 10.39 [95% CI 9.36-11.43]; after 3 months, 3.77 [95% CI 2.52-5.02]) compared with patients in the untreated group (baseline, 10.36 [95% CI 8.98-11.73]; after 3 months, 10.39 [95% CI 8.36-12.42]); MANOVA for time and treatment, *P* = 0.002. Improvement in HRQOL was related to the improvement in psychometry. *Conclusion*: Treatment with lactulose improves both cognitive function and HRQOL in patients with cirrhosis who have MHE. (HEPATOLOGY 2007;45:549-559.)

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Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction diagnosed after exclusion of other known brain diseases. The Working Party at the 11th World Congress of Gastroenterology, Vienna, under the Organization Mondiale de Gastroentrologie proposed a multiaxial definition of HE that defined both the type of hepatic abnormality (type A, B, or C) and the duration and characteristics of neurological manifestations (episodic, persistent, or minimal HE) in chronic liver disease.[1] HE has been considered a continuous dimension that could be measured with 1 index to summarize several neurological domains, such as cognition, emotion, behavior, and biologic rhythms. Minimal hepatic encephalopathy (MHE) represents a portion of this dimension and is the mildest form of HE. Whereas patients with HE have impaired intellectual functioning, personality changes, altered level of consciousness, and neuromuscular dysfunction, patients with MHE have no recognizable clinical symptoms of HE but do have mild cognitive and psychomotor deficits. In the absence of a "gold standard" for determining MHE, neuropsychological (NP) and neurophysiological methods have been the most trusted and widely used tests to diagnose this condition.[1,2]

MHE is considered clinically relevant for at least 3 reasons. First, it impairs patients' daily functioning and

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; FCT, figure connection test; HE, hepatic encephalopathy; HRQOL, health-related quality of life; MHE, minimal hepatic encephalopathy; MANOVA multivariate analysis of variance; NP, neuropsychological; SIP, Sickness Impact Profile.

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Table 1. Clinical and Demographic Characteristics of Patients

	Patients screened (n = 210)	Patients enrolled (n = 90)	NMHE (n = 29)	MHE-NL (n = 30)	MHE-L (n = 31)
Male:female	175:35	80:10	25:4	28:2	27:4
Age (years), mean (range)	47.9 (34.0-75.0)	48.3 (38.4-58.2)	45.4 (37.8-53)	50.6 (39.1-62.1)	48.3 (38.4-58.2)
Education					
Illiterate	14 (6.7%)	6 (6.7%)	2 (6.9%)	3 (10%)	1 (3.2%)
Undergraduate	124 (59.0%)	61 (67.8%)	17 (58.6%)	21 (70%)	23 (74.2%)
Graduate	62 (29.5%)	21 (23.3%)	8 (27.6%)	6 (20%)	7 (22.6%)
Postgraduate	10 (4.8%)	2 (2.2%)	2 (6.9%)	0	0
CTP class					
A	65 (31.0%)	33 (36.7%)	13 (44.8%)	10 (33.3%)	10 (32.3%)
B	101 (48.1%)	45 (50.0%)	12 (41.4%)	17 (56.7%)	16 (51.6%)
C	44 (20.9%)	12 (13.3%)	4 (13.8%)	3 (10%)	5 (16.1%)
Presence of varices	129 (61.4%)	51 (56.7%)	17 (58.6%)	16 (53.3%)	18 (58.1%)
Etiology					
Alcohol	112 (53.4%)	57 (63.3%)	17 (58.6%)	20 (66.7%)	20 (64.5%)
HBV	32 (15.2%)	17 (18.9%)	6 (20.8%)	5 (16.7%)	6 (19.3%)
HCV	30 (14.3%)	11 (12.2%)	4 (13.8%)	4 (13.3%)	3 (9.7%)
Other	36 (17.1%)*	5 (5.6%)†	2 (6.8%)	1 (3.3%)	2 (6.5%)

Abbreviations: CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; NMHE, patients without MHE; MHE-L, patients with MHE who received lactulose therapy; MHE-NL, patients with MHE who have not received lactulose.

*cryptogenic 23, alcohol + HBV or HCV 6, autoimmune 4, and Budd-Chiari syndrome 3.

†cryptogenic cirrhosis 3, autoimmune 1, and Budd-Chiari syndrome 1.

health-related quality of life (HRQOL),[3-5] and many patients with MHE may be unfit to drive a car.[6-8] Second, it predicts the development of overt HE.[9-12] Finally, it is associated with a poor prognosis.[13,14] Thus, MHE may warrant attempts at treatment.

The pathogenesis of MHE is believed to be similar to that of overt HE, and ammonia plays a key role.[15-17] Therapeutic interventions that aim to reduce ammonia are also useful in this setting.[18-24] Most studies have shown improvement in psychomotor functions coupled with a reduction in ammonia level. Improvement in cognitive functions may translate into improvement in HRQOL. Thus far, no study has assessed the effect of therapy on cognitive functions and HRQOL simultaneously in patients with cirrhosis who have MHE. HRQOL has become a key component in the evaluation of any therapeutic intervention. HRQOL questionnaires have been used to study the influence of chronic diseases on daily life.[24-27] The Sickness Impact Profile (SIP) questionnaire, which assesses wide aspects of quality of life, has been used previously to determine the influence of chronic liver disease on patients' daily functioning.[3,26-28] This study was carried out to determine the influence of treatment on psychomotor performance and HRQOL of patients with MHE.

Patients and Methods

The Ethics Committee of Postgraduate Institute of Medical Education and Research (PGIMER), a tertiary-level health care center in Chandigarh, India, approved the study. Each subject gave written informed consent before being included in the study.

Eligibility Criteria. All patients diagnosed as having cirrhosis at the outpatient Liver Clinic of the Department of Hepatology, PGIMER, Chandigarh, were candidates for enrollment. The diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic or liver histological data. Exclusion criteria were overt HE or a history of overt HE; history of recent (<6 weeks) alcohol intake; infection, recent (<6 weeks) antibiotic use or gastrointestinal bleeding; history of recent (<6 weeks) use of drugs affecting psychometric performances like benzodiazepines, antiepileptics, or psychotropic drugs; a history of shunt surgery or transjugular intrahepatic portosystemic shunt for portal hypertension; electrolyte imbalance; renal impairment; hepatocellular carcinoma; severe medical problems such as congestive heart failure, pulmonary disease, or neurological or psychiatric disorder that could influence quality-of-life measurement; and inability to perform NP tests and to complete the SIP questionnaire because of poor vision. Patient characteristics, including educational status, Child-Turcotte-Pugh (CTP) class, and etiology of the cirrhosis, are listed in Table 1.

Male patients were considered to have alcohol-related cirrhosis if daily alcohol intake was more than 80 g and female patients if daily intake was more than 30 g for more than 5 years and if testing showed no viral, metabolic, or immunologic cause.[23] Chronic hepatitis B and C were diagnosed when testing was positive for the viral markers HBsAg and anti-HCV, respectively. None of the

patients received antiviral treatment before or during the study. Autoimmune hepatitis was diagnosed, in an appropriate clinical setting, if one of the autoimmune markers (antinuclear antibody, smooth muscle antibody, or liver kidney microsomal antibody) was positive and liver histology suggested autoimmune hepatitis.[29] The diagnosis of Budd-Chiari syndrome was based on clinical, radiological, and histological findings. Cryptogenic cirrhosis was diagnosed when an extensive etiologic workup did not reveal any possible etiology.[30] All patients underwent a battery of clinical and laboratory investigations and NP tests. In addition, the SIP questionnaire was also administered.

Clinical and Laboratory Assessment. Clinical examination included a thorough general physical examination, taking vitals, and a systemic examination including complete neurological and mental state examination using the Mini Mental State Examination to exclude the presence of any illness that could have caused or affected neurological status or quality of life. The West Haven Criteria for grading mental state in patients with cirrhosis was used to differentiate between grade 0 and grade 1 HE.[31] In addition, special emphasis was given to the absence of disorientation, dysarthria, flapping tremors, increased tone, ataxia, and increased tendon reflexes. Laboratory investigations included a complete hemogram, serum electrolytes, renal and liver function tests, and complete coagulogram. An upper gastrointestinal endoscopy was performed in all patients to determine the presence of esophageal varices. The CTP score was used to assess the severity of liver disease.

Neuropsychological Assessment. The diagnosis of MHE was made with the administration of a combination of quantitative NP tests including 2 number connection tests (NCTs), parts A and B; 2 figure connection tests (FCTs), parts A and B; and 2 performance subtests of the Wechsler Adult Intelligence Scale, the picture completion and block design tests.[32,33] This test combination conforms to the consensus statements of Ferenci et al.[1] These tests were easy to administer and could be performed in 30-40 minutes. In principle, the FCT was similar to the NCT, except that figures were used instead of numbers.[32] The FCT is a universally applicable test for the assessment of mental state that transcends the barriers of illiteracy and linguistic differences. The clinical significance of these tests has been evaluated in a large number of healthy volunteers and patients with MHE.[32] Normal values were derived from 250 healthy volunteers. Different variations of NCTs and FCTs were used for serial evaluation in order to avoid any effect of learning occurring. The NP test results were expressed as *Z* scores, indicating the differences (in standard deviations) between the observed and expected scores given education based on the test results of a large sample of healthy Indian volunteers.[32] Negative values indicated poor performance. A *Z* score less than −2 was considered abnormal.[13,36] A mean *Z* score (mZS) was calculated for each patient in order to avoid bias related to multiple comparisons. Changes in the number of abnormal NP tests and in the mZS after 3 months of treatment or follow-up were referred to as Δabnormal NP tests and ΔmZS, respectively, and served as measures of psychometric change. MHE was diagnosed if 2 or more NP tests were abnormal.[1,9,22,32]

Assessment of Daily Functioning. The SIP questionnaire (Medical Outcome Trust, Boston, MA) was used to assess the influence of disease and treatment on daily functioning.[34] The questionnaire consists of 136 items grouped into 12 scales: sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness, emotional behavior, and communication. Apart from a 12-dimension profile score and physical and psychosocial scores, the SIP provides the opportunity to compute a total score. Each score ranges from 0 (best) to 100 (worst), and patients mark only items that relate to their health at that time. Change in the total SIP score after 3 months of treatment or follow-up was defined as ΔSIP, which served as a measure of change in overall HRQOL.

Patients were given the questionnaire, which was in English, and were asked to read and mark only those questions related to their health at that time. Those subjects who wished to be administered the questionnaire verbally, rather than reading it on their own, had the questions read aloud to them in order listed in the printed questionnaire. For those who did not understand English well and those who were illiterate, an exact Hindi-language translation of the questionnaire (provided by an expert) was read out aloud. Of 90 patients, 76 (84.4%) were able to answer the questionnaire on their own in English; for the rest the Hindi translation was used.

Study Design. Patients who were diagnosed as having MHE were randomly assigned in a 1:1 ratio either to receive lactulose treatment for 3 months (MHE-L group) or not to receive treatment (MHE-NL group, the control). The study was not blinded, and randomization was performed using tables of random numbers. The sequences were concealed (R.K.D.) until a decision to enroll a patient was taken after assessment for eligibility and after receiving informed consent (SP). All subjects were followed up every month for treatment compliance and for development of any complications. In the MHE-L group, patients received 30-60 ml of lactulose in 2 or 3 divided doses so that patient passed 2-3 semisoft stools per

day. Compliance with the therapy was assured primarily by ensuring increased stool frequency and a change to a softer consistency and by counting the number of bottles of lactulose consumed. All patients were assessed for psychometry with NP tests and for daily functioning with the SIP questionnaire at inclusion into the study (0 months) and 3 months after inclusion into the study.

Improvement in MHE and improvement in HRQOL were the primary outcome measures. Endpoints were completion of 3 months of follow-up or development of overt HE.

Dietary Habits and Concurrent Therapy. Most of our patients (~70%) were vegetarian. Protein intake was never restricted in these patients. They predominantly took in vegetable-based or casein-based protein, with a total daily intake of approximately 1 g/kg of body weight. Their diets were routinely supplemented with vitamins. Thirty-nine of the 90 patients (43.3%) (11 with NMHE, 13 with MHE, and 15 with MHE-L) were on salt-restricted diets and a combination diuretic therapy of frusemide and spironolactone. A total of 36 (39.6%) patients (11 with NMHE, 14 with MHE -NL, and 11 with MHE-L) were also receiving β-blockers for prophylaxis of variceal bleed. There was no significant difference in the intake of these medicines among the 3 groups. These medications were continued during the study period.

Statistical Analysis. We calculated that a sample size of at least 23 patients in each arm would be required to detect a difference in improvement in MHE, that is, the proportion of patients with MHE at 3 months, with a 5% type 1 error and 90% power for a 2-tailed log-rank test. On the basis of the results of 3 previous published studies, including one of ours, we estimated an average improvement of 15% in MHE in the control group and an average improvement of 75% in MHE in the treatment group.[21,22,35] Our previous data shows that the prevalence of MHE was 62.4% and 65% and that approximately 15% patients were lost to follow-up.[9,22] Therefore, approximately 26 patients were required in each arm, and it was necessary to enroll a total of 80-90 patients with cirrhosis in order to have the desired number of patients in each arm.

Data are presented as means and 95% confidence intervals (CIs) for quantitative variables and as proportions with 95% CI for qualitative variables.[37,38] ANOVA and post hoc tests were performed to detect overall differences in mean SIP scale values between the various groups. Fisher's exact test was performed to demonstrate improvement in MHE on an intention-to-treat basis. Improvements in NP test variations and SIP scores was studied by MANOVA; the within-groups factor was time (0 and 3 months), and the between-groups factor was treatment (lactulose treatment or no treatment). The relationship between variation in NP tests and total SIP score was assessed by Spearman's rank correlation coefficient. Multivariate analysis using multiple regression was performed to determine the influence of severity of liver disease, etiology of cirrhosis, and educational status. A P value of less than 0.05 was considered statistically significant.

Statistical analysis was performed with SPSS software for Windows, version 10.0 (SPSS Inc., Chicago, IL).

Results

Between January 1, 2004, and February 28, 2005, 210 patients with cirrhosis were screened; 90 patients (42.9%) who met the eligibility criteria were included in the study (Fig. 1). Reasons that the 120 patients (57.1%) were excluded from the study were: history of overt HE (26 patients), history of recent alcohol intake (27 patients), recent infection or antibiotic use (37 patients), recent gastrointestinal bleeding (16 patients), recent use of drugs affecting psychomotor performance (3 patients), shunt surgery (1 patient), renal impairment (1 patient), hepatocellular carcinoma (10 patients), severe medical problem (4 patients), unfit to perform NP tests (2 patients), lactulose or L-ornithine L-aspartate therapy (30 patients), and interferon treatment (3 patients). Several patients were excluded for more than 1 reason: 6 patients were excluded for 3 or more reasons, and 34 were excluded for 2 reasons. The clinical and demographic characteristics of the patients screened and of those enrolled are shown in Table 1. Of the patients included in the study, 80 were men and 10 were women. Table 1 shows the causes of the patients' cirrhosis: alcohol abuse, 57 patients; chronic viral hepatitis, 28 patients; and other causes, 5 patients (autoimmune disorder, 1 patient; Budd-Chiari syndrome, 1 patient; cryptogenic cirrhosis, 3 patients). Most patients whose cirrhosis was caused by alcohol (51 of 57, 89.5%) had been abstaining from alcohol use for more than 6 months.

Sixty-one of the 90 patients with cirrhosis (67.7%) had at least 2 abnormal NP test results. These 61 patients were considered to have MHE, whereas the remaining 29 patients were not considered to have MHE (NMHE). Thirty-one patients who had MHE were assigned to lactulose treatment, whereas the remaining 30 did not receive any treatment (Fig. 1). There were no protocol deviations from the study as planned. The 3 groups (NMHE, MHE-L, and MHE-NL) were comparable in clinical characteristics; sex ratio, age, educational status, CTP class, presence of esophageal varices, and etiology of cirrhosis (Table 1).

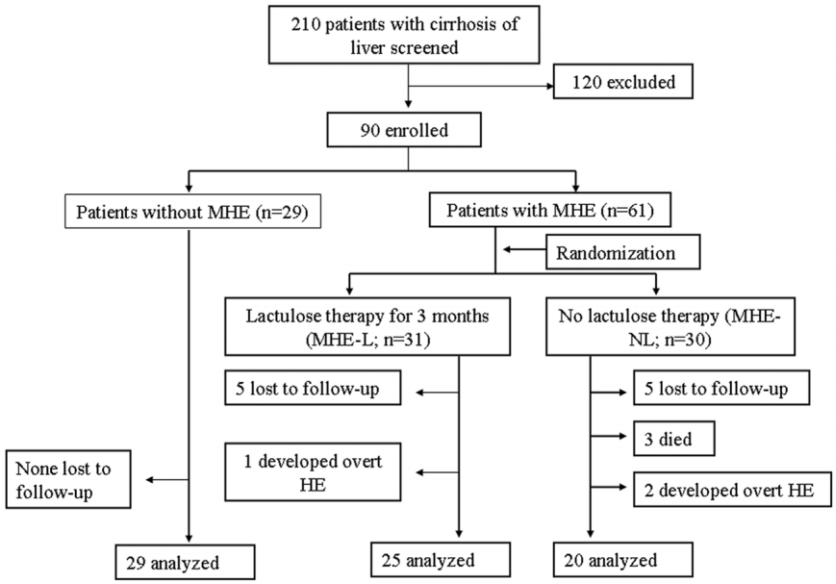

Fig. 1. Flow of participants into the study.

Neuropsychological Evaluation. Table 2 summarizes the mean number of abnormal NP test results in each group. The frequency of an abnormal result of each NP test at baseline was higher in the MHE-L and MHE-NL group patients than in the NMHE group patients (Table 2). The mean number of abnormal NP test results at baseline was significantly higher for the patients in the MHE-NL (2.47, 95% CI 2.19-0.74) and MHE-L (2.74, 95% CI 2.40-3.08) groups than for the patients in the NMHE (.34, 95% CI 0.16-0.53) group ($P < 0.0001$ for both comparisons); however, there was no significant difference between patients in the MHE-NL and MHE-L groups ($P = 0.355$). Similarly, mZS was significantly lower for patients in the MHE-NL (−2.10, 95% CI −1.92-−2.20) and MHE-L (−2.42, 95% CI −2.15-−2.69) groups than for patients in the NMHE (−0.41, 95% CI −0.15-−0.67) group ($P < 0.0001$ for both comparisons; Table 2); however, there was no significant difference between patients in MHE-NL and MHE-L groups ($P = 0.078$). The prevalence of MHE was not higher in patients with cirrhosis caused by alcohol than in patients whose cirrhosis was not caused by alcohol (alcohol, 38 of 57 [66.7%] versus nonalcohol, 23 of 33 [69.7%], $P = 0.951$).

Evaluation of Health-related Quality of Life. Figure 2 shows the mean scores on 12 scales of the SIP of patients with and without MHE at baseline. Patients with MHE showed significant impairment in 11 scales of the SIP, the psychosocial and physical subscores, and in the total SIP

Table 2. Prevalence of Changes in Neuropsychological (NP) Test Results in Each Group

	NMHE (Baseline)	NMHE (After 3 months)	MHE-NL (Baseline)	MHE-NL (After 3 months)	MHE-L (Baseline)	MHE-L (After 3 months)
Number	29	29	30	20	31	25
Abnormal NCT A*	1 (3.7%, .7%-8.3%)	2 (7.4%, 2.1%-23.4%)	10 (37%, 21.5%-55.8%)	7 (38.9%, 20.3%-61.4%)	13 (44.8%, 28.4%-62.4%)	4 (16.7%, 6.7%-35.9%)
Abnormal NCT B*	2 (7.4%, 2.1%-23.4%)	3 (11.1%, 3.9%-28.1%)	17 (63%, 44%-78.5%)	8 (44.4%, 24.6%-66.3%)	17 (58.6%, 40.7%-74.5%)	6 (25%, 12%-44.9%)
Abnormal FCT A	4 (13.8%, 5.5%-30.6%)	3 (10.3%, 3.6%-26.4%)	14 (46.7%, 30.2%-63.9%)	9 (45%, 25.8%-65.8%)	16 (51.6%, 34.8%-68%)	3 (12%, 4.2%-30%)
Abnormal FCT B	3 (10.3%, 3.6%-26.4%)	1 (3.4%, 0.6%-17.2%)	18 (60%, 42.3%-75.4%)	9 (45%, 25.8%-65.8%)	21 (67.7%, 50.1%-81.4%)	2 (8%, 2.2%-25%)
Abnormal picture completion	0 (0%, 0%-11.7%)	0 (0%, 0%-11.7%)	5 (16.7%, 7.3%-33.6%)	9 (45%, 25.8%-65.8%)	2 (6.5%, 1.6%-20.7%)	1 (4%, 0.7%-19.5%)
Abnormal block design	0 (0%, 0%-11.7%)	0 (0%, 0%-11.7%)	8 (26.7%, 14.2%-44.4%)	6 (30%, 14.5%-51.9%)	10 (32.3%, 18.6%-49.9%)	2 (8%, 2.2%-25%)
Number of abnormal NP test results, mean (95% CI)	0.34 (0.16-0.53)[a]	0.31 (0-0.62)[d]	2.47 (2.19-2.74)[b]	2.55 (2.16-2.94)[e]	2.74 (2.40-3.08)[c]	0.75 (0.36-1.16)[f,†]
Mean mZS (95% CI)	−0.41 (−0.15-−0.67)[g]	−0.35 (−0.09-−0.60)[j]	−2.10 (−1.92-−2.20)[h]	−2.34 (−2.06-−2.63)[k]	−2.42 (−2.15-−2.69)[i]	−1.45 (−1.24-−1.66)[l,‡]
Δabnormal NP tests (95% CI)		0.03 (−0.24-0.31)[m]		−0.02 (−0.59-−0.19)[n]		2.00 (1.46 to 2.54)[o]
ΔmZS (95% CI)		0.06 (−0.10-0.22)[p]		−0.27 (−0.55-0.01)[q]		1.02 (.71 to 1.34)[r]
Number of patients with MHE	0	1	30	18	31	5
Development of overt HE	–	0	–	2	–	1

NOTE. Data are expressed as number (percentage with 95% confidence interval); NCT, number connection test; FCT, figure connection test; MHE, minimal hepatic encephalopathy; NMHE, patients without MHE; MHE-NL, patients with MHE who have not had lactulose therapy; MHE-L, patients with MHE who received lactulose therapy; *illiterate patients (2 in the NMHE group, 3 in the MHE-NL group, and 1 in the MHE-L group) did not perform NCTs; Δabnormal NP tests, change in the number of abnormal NP test results between 2 visits; ΔmZS, change in the mZS between 2 visits; improvement following treatment, †$P = 0.001$ and ‡$P = 0.08$ by MANOVA for time and treatment; [ab]$P < 0.0001$; [ac]$P < 0.0001$; [bc]$P = .355$; [de]$P < 0.0001$; [df]P .174; [ef]$P < 0.0001$; [gh]$P < 0.0001$; [gi]$P < 0.0001$; [hi]$P = 0.078$; [jk]$P < 0.0001$; [jl]$P < 0.0001$; [kl]$P < 0.0001$; [mn]$P = 0.724$; [mo]$P < 0.0001$; [no]$P < 0.0001$; [pq]$P = 0.168$; [qr]$P < 0.0001$; [qr]$P < 0.0001$.

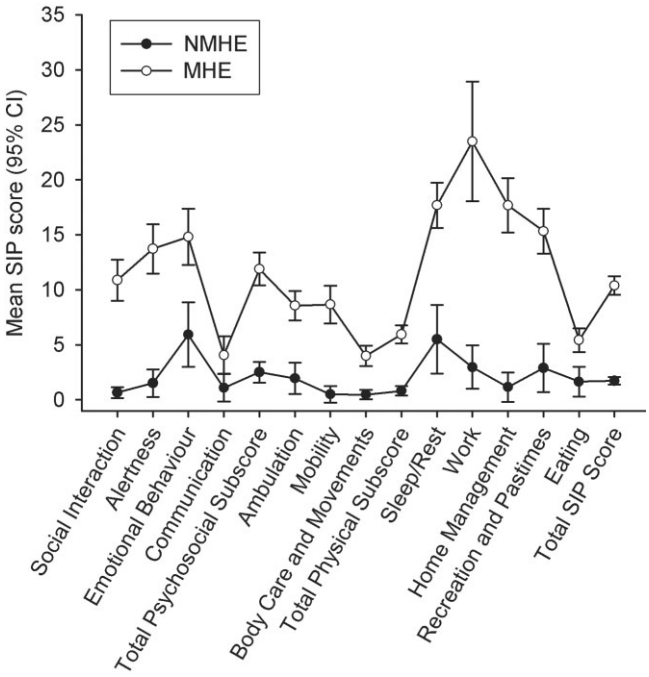

Fig. 2. Mean (95% confidence interval [CI]) SIP scores in patients with cirrhosis with minimal hepatic encephalopathy (MHE) and without MHE (NMHE) at baseline ($P < 0.0001$ for all scales except communication).

score compared with those of the NMHE group patients (Fig. 2). Impairment was much more pronounced in social interaction, alertness, emotional behavior, sleep, work, home management, and recreation and pastimes (Fig. 2).

Among different groups, mean total SIP score at baseline of patients in the MHE-NL (10.36, 95% CI 8.98-11.73) and MHE-L (10.39, 95% CI 9.36-11.43) groups was significantly worse than that of patients in the NMHE (1.73, 95% CI 1.40-2.07) group ($P < 0.0001$ for both comparisons); however, there was no significant difference between patients in the MHE-NL and MHE-L groups ($P = 0.998$; Table 3). Mean scores on all 12 scales of the SIP, the psychosocial subscore, and the physical subscore were also not significantly different between MHE-L and MHE-NL group patients at baseline but were worse than those of the patients in NMHE group (Table 3).

Possible confounders of the HRQOL analysis that compared patients with and without MHE are severity of liver disease (CTP score, presence of varices), etiology of cirrhosis (alcohol versus nonalcohol), and educational status. Therefore, these variables were selected for multivariate analysis to evaluate their impact on total SIP score. Factors considered for analyses were MHE (presence or absence), CTP (class A versus class B or C), varices (presence or absence), education level (less than a graduate versus a graduate or more), and etiology (alcohol versus nonalcohol at baseline). Analysis showed that only the presence of MHE significantly affected total SIP score (Table 4).

Impact of Lactulose Therapy on NP Test Results. The mean number of abnormal NP test results decreased

Table 3. Sickness Impact Profile Scores of Patients in Different Groups at Baseline (0 Months) and After 3 Months of Follow-Up

	NMHE		MHE-NL		MHE-L	
	0 Months (n = 29)	3 Months (n = 29)	0 Months (n = 30)	3 Months (n = 20)	0 Months (n = 31)	3 Months (n = 25)
Psychosocial scales						
Social interactions	0.66 (0.16-1.16)	0.83 (0.23-1.44)	9.87 (6.78-12.95)	10.18 (5.62-14.73)	11.88 (9.51-14.17)	3.06 (1.47-4.66)
Alertness	1.51 (.25-2.77)	0.90 (−.09-1.88)	12.32 (8.52-16.12)	14.22 (8.62-19.83)	15.07 (12.47-17.67)	5.42 (2.40-8.44)
Emotional behavior	5.93 (3.00-8.86)	6.01 (3.03-8.99)	15.97 (12.34-19.59)	15.78 (10.90-20.66)	13.68 (9.89-17.47)	3.53 (1.25-5.82)*
Communication	1.09 (−.16-2.35)	0.30 (−.32-0.93)	4.39 (1.62-7.15)	4.39 (.85-7.92)	3.77 (1.60-5.94)	1.16 (−0.18-2.50)
Total psychological subscore	2.51 (1.57-3.46)	2.20 (1.31-3.09)	11.63 (8.92-14.34)	12.19 (8.42-15.95)	12.13 (10.66-13.60)	3.60 (2.14-5.07)*
Physical scales						
Ambulation	1.95 (0.52-3.38)	2.35 (1.10-3.60)	9.07 (6.84-11.29)	11.19 (8.24-14.14)	8.08 (6.47-9.70)	4.54 (2.96-6.11)*
Mobility	0.51 (−0.24-1.26)	0.96 (0.02-1.91)	9.26 (6.41-12.11)	8.09 (5.48-10.71)	8.07 (5.99-10.16)	3.40 (1.56-5.24)*
Body care and movements	0.48 (0.04-0.91)	0.20 (−0.09-0.49)	4.39 (3.07-5.71)	2.81 (1.47-4.16)	3.61 (2.23-4.99)	1.86 (0.30-3.42)
Total physical subscore	0.82 (.39-1.25)	0.99 (0.62-1.35)	6.37 (5.07-7.68)	6.20 (4.64-7.76)	5.55 (4.52-6.57)	2.75 (1.7-3.79)*
Independent scales						
Sleep/rest	5.51 (2.39-8.62)	3.30 (0.98-5.63)	19.15 (16.00-22.31)	16.27 (11.16-21.39)	16.26 (13.55-18.98)	7.01 (4.20-9.82)*
Work	2.97 (1.00-4.95)	0.99 (−0.16-2.14)	22.80 (15.20-30.39)	21.27 (12.65-29.89)	24.19 (15.94-32.43)	9.36 (1.57-17.14)
Home management	1.15 (−0.19-2.48)	1.50 (0.19-2.81)	16.09 (12.68-19.49)	16.25 (10.70-21.80)	19.20 (15.52-22.87)	7.49 (4.35-10.62)
Recreation and pastimes	2.89 (0.70-5.09)	3.56 (1.30-5.83)	15.18 (12.03-18.33)	16.58 (11.05-22.10)	15.48 (12.63-18.42)	3.81 (0.95-6.67)*
Eating	1.65 (0.29-3.02)	1.37 (0.41-2.34)	5.69 (3.68-7.69)	5.33 (0.61-10.04)	5.16 (4.21-6.10)	1.26 (0.32-2.20)
Total SIP score	1.73 (1.40-2.07)	1.52 (1.18-1.85)	10.36 (8.98-11.73)	10.39 (8.36-12.42)	10.39 (9.36-11.43)	3.77 (2.52-5.02)*
ΔSIP		0.22 (−0.13-0.57)[a]		0.17 (−0.29-0.63)[b]		6.81 (5.24-8.37)[c]

NOTE. Data are expressed as means (95% confidence interval)s; MHE, minimal hepatic encephalopathy; NMHE, patients without MHE; MHE-NL, patients with MHE who have not had lactulose therapy; MHE-L, patients with MHE who received lactulose therapy; SIP, Sickness Impact Profile; *significant improvement in patients in the treated group after 3 months of lactulose treatment (n = 25) compared with patients in the untreated group after 3 months of follow up (n = 20) in the following scores (by MANOVA for time and treatment)—emotional behavior ($P < 0.0001$), ambulation ($P = 0.008$), mobility ($P = 0.049$), sleep/rest ($P = 0.013$), recreation and pastimes ($P = 0.007$), total psychosocial ($P = 0.01$) and physical ($P = 0.029$) subscores, and total SIP score ($P = 0.002$); ΔSIP, change in total SIP score between 2 visits; [ab]$P = 0.998$; [ac]$P < 0.0001$; [bc]$P < 0.0001$.

Table 4. Effects of Minimal Hepatic Encephalopathy, CTP Class, Esophageal Varices, Etiology of Cirrhosis, and Educational Status on Total SIP Score at Baseline

Variable	Regression coefficient	Standard error	*P* value
Minimal hepatic encephalopathy	8.508	0.620	< 0.0001
CTP class (A versus B plus C)	0.005	0.607	0.993
Presence of esophageal varices	0.501	0.579	0.389
Etiology (alcohol versus nonalcohol)	0.993	0.595	0.098
Educational status (not graduated versus graduated or higher)	0.910	0.672	0.178

Abbreviations: CTP, Child-Turcotte-Pugh; SIP, Sickness Impact Profile.

significantly among patients in the MHE-L group after 3 months of treatment (0 months, 2.74 [95% CI 2.40-3.08]; 3 months, .75 [95% CI .36-1.16]) compared with patients in the MHE-NL group after 3 months of follow-up (0 months, 2.47 [95% CI 2.19-2.74]; 3 months, 2.55 [95% CI 2.16-2.94]); MANOVA for time and treatment, $P = 0.001$ (Table 2). The number of abnormal results for each test decreased only in the MHE-L group patients after 3 months of lactulose therapy (Table 2). The Δabnormal NP tests was also significantly higher in the MHE-L group than in the MHE-NL group (2.00, 95% CI 1.46-2.54; versus −.02, 95% CI −.59-0.19; $P < 0.0001$), indicating significant improvement in cognitive function in the treated group (Table 2). There was a trend toward improvement in the mZS of the MHE-L group patients after 3 months of lactulose therapy compared with patients in the MHE-NL group (MANOVA for time and treatment, $P = 0.080$; Table 2). The number of abnormal NP test results and the mZS of patients in the NMHE group did not change significantly (Table 2). Intention-to-treat analysis showed that improvement following lactulose therapy was significant. Whereas 20 of the 31 patients (64.5%) in the MHE-L group improved, 2 of the 30 patients (6.7%) in the MHE-NL group so (Fisher's exact test; $P < 0.0001$). One patient in the MHE-L group and 2 patients in the MHE-NL group developed overt HE ($P = 0.976$). One of the 29 patients in the NMHE group was found to have developed MHE on follow-up.

None of the patients reported side effects related to lactulose therapy.

Impact of Lactulose Therapy on Health-Related Quality of Life. Tables 3 and 5 show the impact of treatment with lactulose on the SIP profile score. Group-specific mean changes (Δ) in the 10 SIP scale scores between the 2 visits were significantly higher in the MHE-L group than in the MHE-L group (Table 5). The total SIP score of patients in the MHE-NL group improved after 3 months of therapy (0 months, 10.39 [95% CI 9.36-11.43]; 3 months, 3.77 [95% CI 2.52-5.02]); however there was no significant change in patients in the MHE-NL group after 3 months (0 months, 10.36 [95% CI 8.98-11.73]; 3 months, 10.39 [95% CI 8.36-12.42]); MANOVA for time and treatment; $P = 0.002$ (Table 3). Using MANOVA for time and treatment, significant improvement in score by patients in the treated group was found in only 5 of the 12 scales of the SIP and in the total psychosocial and physical subscores compared to those of patients in the untreated group (Table 3). The improvement was significant in emotional behavior, ambulation, mobility, sleep/rest, and recreation and pastimes. The SIP scores of patients in the NMHE group did not change significantly after 3 months (Table 3).

Correlation of NP Test Results with Total SIP Score. The NP test results correlated with total SIP score, and psychometric change (Δabnormal NP tests and ΔmZS) correlated with ΔSIP (Table 6). The correlations between NP test results and total SIP score persisted after 3 months of follow-up. In another multivariate analysis, Δabnormal NP tests but not severity of liver disease, etiology of cirrhosis, or educational status, affected the ΔSIP (regression coefficient 1.569, standard error 0.283, $P < 0.0001$ for Δabnormal NP tests; *P* values for other variables: CTP = 0.131, esophageal varices = 0.842, education = 0.456, etiology = 0.598).

Discussion

This study confirmed the high prevalence of MHE among patients with cirrhosis. Patients with cirrhosis who had MHE showed impaired daily functioning. Multivariate analysis that took into account the severity of liver disease, educational status of the patient, and etiology of cirrhosis showed that MHE was independently related to a diminished HRQOL. Three months of therapy with lactulose resulted in improvement in MHE (cognitive functions) and in the total SIP score. The improved SIP score was linked to improvement in NP test results.

The prevalence of MHE in our outpatient population of patients with cirrhosis was 67.7%. Similar percentages were found in our previous studies[9,22,32] and in studies by other investigators.[23,39] The prevalence of MHE has been reported to vary between 30% and 84% in patients with liver cirrhosis.[40] The major difficulty in diagnosing MHE has been not having a precisely defined gold standard for determining this disorder. The large variation in prevalence found in different studies is related to the criteria used to diagnose MHE and to the patient populations studied. The results of NP tests can be influenced by variables such as age, educational status, and learning effects. There were fewer patients older than 60 years in this

Table 5. Group-Specific Mean Changes (Δ) in Various SIP Scales Between 2 Visits Among Patients in MHE-NL and MHE-L Groups

	MHE-NL (n = 20)	MHE-L (n = 25)	*P* value
Psychosocial scales			
Social interactions	0.50 (−0.84-1.84)	8.50 (5.86-11.14)	< .0001
Alertness	−0.75 (−2.97-1.46)	10.43 (7.04-13.82)	< .0001
Emotional behavior	2.76 (−.82-6.34)	8.98 (5.93-12.02)	0.009
Communication	0.75 (1.59-3.09)	2.66 (0.28-5.05)	0.061
Total psychological subscore	0.77 (−0.05-1.58)	8.47 (6.55-10.39)	< 0.0001
Physical scales			
Ambulation	−1.89 (−4.09-0.30)	3.67 (2.11-5.24)	< 0.0001
Mobility	1.22 (−1.09-3.54)	5.36 (2.71-8.00)	0.017
Body care and movements	0.72 (−0.11-1.55)	1.62 (0.54-2.69)	0.292
Total physical subscore	0.01 (−1.00-1.03)	2.99 (1.88-4.09)	< 0.0001
Independent scales			
Sleep/rest	2.29 (−0.34-4.93)	9.04 (5.21-12.87)	0.031
Work	−0.06 (−2.87-2.75)	15.83 (7.10-24.56)	0.001
Home management	0.94 (−1.4-3.27)	12.64 (7.32-17.96)	< 0.0001
Recreation and pastimes	−0.28 (−2.47-1.90)	11.59 (7.73-15.46)	< 0.0001
Eating	−0.56 (−3.13-2.01)	3.88 (2.51-6.25)	0.002
Total SIP score	0.17 (−0.29-0.63)	6.81 (5.24-8.37)	< 0.0001

NOTE. Data are expressed as means (95% confidence intervals); negative values indicate poor performance; Δ, change in various SIP scores between 2 visits.
Abbreviation: SIP, Sickness Impact Profile.

study, who could show the effect of age on MHE prevalence. Our previous observations showed that age less than 60 years did not significantly influence psychometric performance.[32] We used adjusted *Z* scores for education and different variations in NCTs and FCTs in order to avoid any effect of education and of learning. The prevalence of MHE was reported to be higher in patients with cirrhosis with CTP classes B and C, advanced age, alcoholic etiology, a previous episode of overt HE, and portosystemic shunts.[41] None of the patients in this study had a previous episode of overt HE or had undergone portosystemic shunt surgery. Alcohol etiology is unlikely to influence the prevalence of MHE, because most patients (~90%) with alcohol etiology had been abstaining from alcohol for more than 6 months, and there was no difference in the presence of MHE according to alcohol etiology. As we demonstrated previously, we did not find that etiology or CTP class affected the prevalence of MHE.[9]

The results of this study confirmed the negative impact of MHE on HRQOL, as patients had impaired results for 11 of the 12 scales of the SIP questionnaire. The patients with MHE showed impairment in perception, memory, learning, expression (language, constructive abilities, and voluntary motor control), mental activity (attention, mental speed), and executive function.[41,42] Attention, executive function, speed of information processing, and visual spatial functions of our patients were affected as assessed by NP tests, which may have been responsible for the impairment found in several of the domains of SIP

Table 6. Correlation of Total SIP Score with NP Tests

	Baseline (0 months)		After 3 months	
	*r**	*P* value	*r**	*P* value
Correlation of total SIP score with				
NCT-A *Z* score	−0.539	< 0.0001	−0.490	< 0.0001
NCT-B *Z* score	−0.589	< 0.0001	−0.441	0.004
FCT-A *Z* score	−0.255	0.015	−0.316	0.031
FCT-B *Z* score	−0.556	< 0.0001	−0.561	< 0.0001
Picture completion *Z* score	−0.552	< 0.0001	−0.624	< 0.0001
Block design *Z* score	−0.505	< 0.0001	−0.518	< 0.0001
Number of abnormal psychometric tests	0.625	< 0.0001	0.544	< 0.0001
mZS	−0.614	< 0.0001	−0.614	< 0.0001
ΔSIP and Δabnormal NP tests	–	–	0.486	< 0.0001
ΔSIP and ΔmZS	–	–	−0.460	< 0.0001

**r,* Spearman's rank correlation coefficient (2-tailed); NCT, number connection test; FCT, figure connection test; NP, neuropsychological; ZS, *Z* score; mZS, mean *Z* score; ΔSIP, change in total SIP score between 2 visits;Δabnormal NP tests, change in number of abnormal NP test results between 2 visits; ΔmZS, change in mZS between 2 visits.

questionnaire. There is also compelling evidence in the literature that impact of impaired cognitive functioning on patients' daily functioning and well-being may be enormous.[3-8] Using the SIP questionnaire, Tarter et al.[43] reported finding more impairment in SIP categories by patients with cirrhosis than by the controls. However, in this study no distinction was found in patients with cirrhosis according to MHE status. Subsequently, Groenweg et al.[3] confirmed that a diminished level of daily functioning was more frequently related to alertness, social interactions, recreation, and work in stable patients with cirrhosis who had MHE. The impact of MHE on patients' daily functioning was further illustrated by 50% of the patients with MHE not having regular employment, compared to only 15% of the patients without MHE.[44] This is in agreement with the results of another study, which found that 44% of patients with MHE were unfit to work.[5] In addition, the psychomotor defects found in MHE could have a negative effect on fitness to drive an automobile.[6,7] On the basis of NP test results, Schomerus et al.[7] considered 60% of their patients with cirrhosis to be unfit to drive. Using a standardized 90-minute on-the-road driving test, Wein et al.[8] reported that fitness to drive a car was impaired in patients with cirrhosis who had MHE; patients with MHE had the worst ratings, whereas patients without MHE had scores similar to those of the controls. These observations strongly suggest that MHE should be considered a medical condition that might warrant treatment in order to decrease psychomotor impairment and improve HRQOL.[45]

In this study, we observed concomitant improvement in cognitive functions and HRQOL in MHE patients following lactulose therapy. The improvement in abnormal NP test results (semiquantitative estimation) was significant; however, improvement in the mZS (quantitative) did not reach a significant level, which could be related to having an inadequate number of patients on follow-up. Nevertheless, the persistence of a significantly strong correlation of NP test results with SIP score, with patients with MHE showing improvement after lactulose therapy, further confirms that improvement in HRQOL was linked to improvement in cognitive functions. Improvement was noted in emotional behavior, ambulation, mobility, sleep/rest, and recreation and pastimes. There may be several cognitive complaints that may be particularly related to having MHE[44] and may show improvement with treatment. This will be the subject of our future study involving a larger number of patients. We used the generic, non-disease-specific quality-of-life SIP questionnaire, which enabled measuring the global impact of MHE on the patients' well-being. Disease-specific measures for cirrhosis are more useful in targeting issues relevant to patients with a particular condition and are more responsive and may also capture small but clinically important changes occurring as a result of therapy or natural progression of the disease. There is a necessity to develop a new, disease-specific clinical scale for the assessment of specific combinations of clinical neuropsychiatric symptoms (cognitive questions) in MHE. Future studies evaluating the impact of therapy on HRQOL in patients with cirrhosis who have MHE should therefore use either generic and such disease-specific instruments or tools that combine generic and disease-specific scales because each complements the other.

Ammonia is the key factor in the pathogenesis of overt HE in patients with cirrhosis. Several lines of evidence suggest that the pathogenesis of MHE is similar to that of overt HE.[15-17] Several treatment modalities that reduce ammonia level have been tried in order to treat this condition, for example, dietary protein manipulation,[18] branched-chain amino acids,[19] L-ornithine L-aspartate,[20] lactulose,[21,22,46] and probiotics.[23] Most of the studies of these treatment modalities have found improvement in psychometry,[19-23] ammonia level,[20,23,24] and cerebral edema.[46] We did not measure ammonia level in our patients; however, we believe that improvement in the MHE in our patients most likely was related to the same mechanism. Lactulose was chosen as a modality of intervention in this study because the drug is cost effective, easily available, and effective in reducing blood ammonia.[47,48] In a recent systematic review, Als-Nielsen et al.[49] concluded there is insufficient evidence to support or refute use of nonabsorbable diasaccharides for HE. However, the inconclusive results of these studies could be related to confounding factors, such as precipitating events, degree of hepatic failure, and extent of portosystemic shunting.[50] Therefore, it is essential to identify a homogenous group of patients who have the least number of confounding variables and might yield clear results. One such group of patients may be those with MHE, who might benefit from treatment with lactulose. In this study, all our patients were clinically stable and as a group were very homogenous, because those with characteristics that might have confounded the results were excluded from the study. We therefore believe that improvement in the MHE of our patients following lactulose treatment reflects the true efficacy of lactulose. Spontaneous resolution of MHE was seen in 2 patients (6.7%) in the MHE-NL group, which was lower than the 12.5% that we reported previously.[9] This may be related to a shorter follow-up of patients in this study.

The major limitation of this study was that the investigator performing the psychometric testing and admin-

istering the SIP questionnaire was not blinded to the treatment. Therefore, treatment bias could not be totally excluded. However, the effect of such bias, if any, would be very small because of the objective nature of the NP tests and the use of the standardized SIP questionnaire.

We conclude that patients with cirrhosis who have MHE showed impairment in daily functioning as assessed by SIP. Treatment with lactulose improved both cognitive functions and HRQOL. Therefore, patients with cirrhosis who have MHE who are at occupational risk, for example, handling heavy machines or unfit to drive, may benefit from treatment. Whether treatment also prevents or delays progression to overt HE and improves prognosis remains to be determined in prospective studies.

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