

# Minimal hepatic encephalopathy runs a fluctuating course: results from a three-year prospective cohort follow-up study

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## ABSTRACT

**Introduction:** Minimal hepatic encephalopathy (mHE) has been reported in up to 84 percent of cirrhotics. The natural history of mHE has not been well-described. We designed a three-year prospective cohort study to determine the prevalence and natural history of mHE among cirrhotic patients.

**Methods:** The patient cohort comprising 62 consecutive outpatients with cirrhosis were assessed at baseline and followed-up with a repeat assessment three years later. The assessments include: (1) Neuropsychometric analysis (digit-symbol substitution test, block-design test, number-connection test A); (2) Clinical, biochemical assessment; and (3) Quality of life (QOL) assessment (abbreviated sickness impact profile).

**Results:** Baseline characteristics were: age 52.9 +/- 11.0 years; Child's A:B:C was 46:14:2. mHE was detected in 33.9 percent of the cohort. Older age, a higher Child-Pugh score and female gender were independently associated with mHE. mHE was associated with a poorer QOL. Follow-up assessment three years later showed that seven patients had died, while six were lost to follow-up; these patients had significantly higher baseline Child's scores. Of the remaining patients, 36/49 (73 percent) agreed to a repeat evaluation. In this group, none had mHE. QOL remained impaired despite the resolution of mHE.

**Conclusion:** It has been shown for the first time that mHE can revert to a normal state in a significant proportion of patients with well-compensated cirrhosis.

**Keywords:** cirrhosis, hepatic encephalopathy, minimal hepatic encephalopathy

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## INTRODUCTION

Minimal hepatic encephalopathy (mHE), previously termed as subclinical hepatic encephalopathy, is a condition in which cirrhotic patients have a normal neurological examination, yet demonstrate quantifiable neuropsychological defects.<sup>(1)</sup> More than 30 years after this "subclinical" state was first described, we still lack a gold standard in diagnosing the condition.<sup>(2)</sup> The incidence of mHE has been reported in as many as 20%–84% of cirrhotics, depending on which methods or tools are used.<sup>(3-5)</sup> It has been well-described that mHE has a subtle but negative impact on a patient's spatial skills, motor skills and even quality of life.<sup>(6-8)</sup> This form of encephalopathy is also known to improve with treatment, such as with non-absorbable disaccharides.<sup>(9,10)</sup> Its negative impact on daily living, among other reasons, has led some authors to suggest that the failure to diagnose this condition could be classified as a medical error.<sup>(11,12)</sup> However, the natural history of mHE is not well-described. In earlier studies, overt hepatic encephalopathy (HE) was subsequently found in patients with previously-documented mHE. However, most study samples were small and their follow-up periods short.<sup>(13-15)</sup> Few studies on mHE have been conducted with the primary aim of assessing its natural history. We therefore designed a prospective three-year cohort follow-up study to determine the prevalence, risk factors and natural history of mHE among patients with cirrhosis.

## METHODS

This was a three-year prospective cohort follow-up study, conducted in a tertiary care hospital. The study was approved by the institutional review board of the hospital. The patient cohort comprised consecutive patients with cirrhosis of the liver and who attended the outpatient services over a four-week period in August 2001. The diagnosis of liver cirrhosis was based either on histology or supporting imaging studies together with history and physical examination. Patients with overt encephalopathy, mental deficiency, sensory or motor deficits, illiteracy, neurological causes of impaired cognition, ongoing systemic illnesses, electrolyte imbalances, or active alcohol or substance abuse were excluded from this study. Informed consent was obtained

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**Table I. Abbreviated sickness impact profile questionnaire.**

Category	Statement
Ambulation	1. I walk more slowly. 2. I walk shorter distances or stop to rest more often. 3. I walk by myself but with some difficulty; e.g. limp, wobble, stumble, have a stiff leg.
Mobility	4. I stay in bed more. 5. I stay in bed most of the time. 6. I stay away from home only for brief periods of time.
Body care / movement	7. I do not fasten my clothing; e.g. requires assistance with buttons, zippers, shoelaces. 8. I stand only for short periods of time. 9. I change position frequently. 10. I do not have control of my bowels. 11. I have trouble getting shoes, socks or stockings on.
Social interaction	12. My sexual activity is decreased. 13. I am going out less to visit people. 14. I am cutting down the length of visits with friends. 15. I often express concern over what might be happening to my health. 16. I stay alone much of the time. 17. I show less interest in other people's problems; e.g. don't listen when they tell me about their problems, don't offer help.
Alertness	18. I am confused and start several actions at a time. 19. I react slowly to things that are said or done. 20. I sometimes behave as if I were confused or disorientated in place or time; e.g. where I am, who is around, directions, what day it is. 21. I forget a lot; e.g. things that happened recently, where I put things, appointments. 22. I do not keep my attention on any activity for long.
Emotional behaviour	23. I am irritable and impatient with myself; e.g. talk badly about myself, swear at myself for things that happen. 24. I often moan and groan in pain or discomfort. 25. I keep rubbing or holding areas of my body that hurt or are uncomfortable.
Communication	26. I am having trouble writing or typing.
Sleep and rest	27. I sleep or doze most of the time – day and night. 28. I spend much of the day lying down in order to rest. 29. I lie down more often during the day in order to rest.
Home management	30. I am not doing any of the regular work around the house that I would usually do. 31. I have difficulty doing handiwork; e.g. turning on faucets, using kitchen gadgets, sewing, carpentry. 32. I am not doing any of the clothes washing that I would usually do.
Recreation / pastime	33. I am cutting down on some of my usual inactive recreation and pastimes; e.g. watching TV, playing cards, reading. 34. I am going out for entertainment less often. 35. I am not doing any of my usual physical recreation or activities.
Work	36. I am not working at all.

and each patient was evaluated on the same day or within two weeks of the date of consent. 62 patients provided their informed consent and were eligible for evaluation.

The neuropsychometric tests employed were the number connection test-A (NCT-A), block-design test (BDT) and the digit-symbol substitution test (DST). All neuropsychometric tests were conducted with a “lead-in” of mock examples for patients, before proceeding to the test proper with scoring. This was to ensure that patients had a full understanding of the test instructions, reducing the possibility of false positive results. Results were assessed against values which have been validated in a local population and corrected for educational level and age. The tests were conducted by one of three investigators and conformed to standard the conditions (i.e. the test

was conducted on a one-to-one basis in a quiet room with sufficient light). All tests were conducted in the subjects' spoken language. mHE was defined as the presence of any one abnormal neuropsychometric test result.

The patients' quality of life (QOL) was assessed using an abbreviated version of the original sickness impact profile (SIP) questionnaire. This questionnaire covers the following basic areas of life, viz. ambulation, mobility, alertness, sleep and rest, body care, home management, emotional behaviour, communication, recreation, work and social interaction (Table I). The questionnaire was administered in the subjects' spoken language. All patients had a venous ammonia level tested at baseline. Three years later, the patients were recalled to undergo the same battery of neuropsychometric tests to assess for the presence of

mHE. The abbreviated SIP questionnaire was administered again to re-assess their QOL. These tests were administered by the same investigators under the same conditions. None of the study patients were specifically treated for mHE within the study period (e.g. with lactulose).

Data was analysed using the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). Comparisons between patients with mHE and those without mHE were done using the Student's *t*-test (for parametric variables), Mann-Whitney U test (for non-parametric variables) and by chi-square or Fisher's exact test (for categorical outcomes). Comparisons between patients with mHE at baseline and their outcomes three years later were performed using paired *t*-test (for parametric variables), Wilcoxon Rank Sum test (for non-parametric variables) and McNemar chi-square test (for categorical outcomes). In analysing for prognostic variables, univariate analysis was first performed and the prognostic variables identified from this analysis were then subjected to multivariate analysis to identify the independent prognostic factors by logistic regression. A *p*-value of less than 0.05 was defined as achieving statistical significance.

## RESULTS

62 patients were tested at baseline. Table II summarises the baseline characteristics of this cohort. mHE was found in 33.9% of patients (Table III). Patients without mHE had a statistically significant lower mean age and lower Child-Pugh scores. Patients with mHE had more outpatient attendances per year and had longer inpatient hospitalisation days per year. There was no difference or correlation in ammonia levels between those with or without mHE. Multivariate analysis confirmed that older age, female gender and a higher Child-Pugh score were independent predictors of the presence of mHE. Aetiology of cirrhosis was not a predictor of mHE. mHE was associated with an impaired QOL, especially in the areas of alertness (poor attention spans and dozing off easily), social interaction (visiting others less), mobility (walking more slowly) and work (stopped working). Three years after the initial evaluation, seven patients had died and six were lost to follow-up. Of the remaining 49 patients, 36 consented to and 13 patients declined a repeat evaluation.

The characteristics of the patients who consented to a repeat evaluation were not significantly different from those who declined evaluation. Overall, there was no difference in the age ( $49.6 \pm 11.3$  vs.  $52.5 \pm 11.4$  years), gender (73% vs. 66% males) and Child's grade (89% vs. 86% Child's A) between those who declined and those who consented to a repeat study. The characteristics at baseline and at three years for the 36 patients who underwent re-evaluation are

**Table II. Baseline characteristics of patients.**

Characteristic	Value (n = 62)
No. of male : female patients	44 : 18
No. of Chinese : Indian : Malay	58 : 3 : 1
Mean and SD age (years)	$52.9 \pm 11.0$
Aetiology of liver disease (%)	
Hepatitis B	71.0
Hepatitis C	1.6
Alcohol	8.1
Miscellaneous	19.4
Status of liver disease	
Child-Pugh score	$5.8 \pm 1.4$
Child's A : B : C (no. of patients)	46 : 14 : 2

SD: standard deviation

**Table III. Incidence of minimal hepatic encephalopathy at baseline.**

	With mHE	Without mHE	<i>p</i> -value
No. (%) of patients	21 (33.9)	41 (76.1)	
No. of male : female patients	11 : 10	33 : 8	0.02
Mean and SD age (years)	$59.4 \pm 8.9$	$48.4 \pm 11.4$	0.02
Child-Pugh score	$6.6 \pm 1.9$	$5.4 \pm 0.9$	0.002
Child's grade (%)			
A	28.3	71.7	
B	42.9	57.1	
C	100	0	
Ascites (%)	38.1	9.8	0.02
Driving (%)	33.3	65.9	0.02
Motor accidents	0	7.3	0.55
No. of hospital attendances			
Outpatient visits/year	$5.2 \pm 3.0$	$3.8 \pm 2.7$	0.05
Inpatient days/year	$3.0 \pm 5.7$	$0.8 \pm 2.2$	0.04
Ammonia (umol/L)	$22.9 \pm 21.7$	$23.1 \pm 15.9$	0.98

SD: standard deviation

summarised in Table IV. None of the re-evaluated patients were active alcohol abusers. The re-tested group of patients scored slightly better on the NCT-A, but there was no significant difference in the test scores for either the BDT or the DST. Among the patients in the re-test group, 20% of them originally had mHE at baseline. Comparing the QOL among the patients who originally had mHE which was then resolved after three years, it was found that these patients reported impairment in the areas of alertness (more forgetful) and social interaction (going out less and entertaining less) at the follow-up evaluation in the third year. They also reported that they felt intermittent periods of confusion. In these patients, their Child's score had decreased by a mean of 0.5. The QOL among the patients who did not have mHE both at baseline and three years later was also impaired. This was also in the domains of alertness and social interaction. In addition, their emotions were also affected, as most reported that they were worrying more about their health three years later.

**Table IV. Characteristics and results of cirrhotic patients who consented to a repeat evaluation for minimal hepatic encephalopathy.**

	Baseline	Three years later	p-value
No. of patients	36	36	
Mean and SD age (years)	53 ± 11	55.0 ± 10	–
No. of male : female patients	24 : 12	24 : 12	
Aetiology of liver disease			
Viral : alcohol (%)	75 : 2	75 : 2	–
Mean Child-Pugh score	5.4 ± 0.9	5.4 ± 1.0	0.96
No. of Child's grade			
A : B : C	31 : 5 : 0	32 : 4 : 0	0.72
Psychometric test scores			
NCT-A (secs)	45 ± 23	37 ± 13	0.10
BDT	32 ± 12	30 ± 9	0.66
DST	38 ± 15	36 ± 9	0.64
No. (%) patients with mHE	7 (20)	0 (0)	

SD: standard deviation; NCT-A: number connection test-A; BDT: block-design test; DST: digit-symbol substitution test.

In this cohort, the mortality at three years was 11%. Mortality was associated with a higher Child-Pugh score. Among the patients who died, more had documented mHE at baseline, although this incidence was not statistically significant. There was no statistical difference in age, gender distribution, educational level or aetiology of cirrhosis between the patients who survived and those who had died. Only one patient in this study exhibited overt HE during the study period. She had two episodes of HE, both of which were believed to have been precipitated by an infection. However, she tested negative for mHE both at baseline and at the end of our study.

## DISCUSSION

Our prospective cohort study evaluated the natural history of mHE in a group of patients with predominantly well-compensated cirrhosis of viral aetiology. The incidence of mHE was 34%. After three years, evaluation of the 73% of patients still under follow-up (11% died and 10% were lost to follow-up) found resolution of mHE in all of them, indicating that mHE is not a permanent disorder. In addition, overt HE did not develop in this group, except for the one patient mentioned above.

As is the major limitation in any study on mHE, there is no standard definition or diagnostic criteria for this condition. There exist over 65 different diagnostic tests which can be used for screening, inclusive of both neuropsychological and neurophysiological tests.<sup>(5)</sup> Furthermore, the various studies on mHE, to date, have used arbitrary cut-off points to declare the presence or absence of the condition. In our study, we have defined the presence of mHE as at least one abnormal neuropsychometric test, as has been done in most other studies.<sup>(5,6,15-18)</sup> We chose this cut-off for ease of comparison with other study results

and to reduce the possibility of false-negatives in our data, especially as the majority of the study subjects were Child's A cirrhotics. Among the wide variety of psychometric tests available, we selected those that have been used more commonly in other studies.<sup>(19)</sup>

Previous studies primarily evaluating the natural history of mHE are limited. Also, earlier studies tended to have short follow-up periods.<sup>(13-15)</sup> A study by Yen and Liaw was conducted on patients with advanced decompensated cirrhosis. 25 of 44 cirrhotic patients were found to have mHE by abnormal number connection test or altered somatosensory-evoked potentials. 18 of these patients developed overt HE at six months of follow-up.<sup>(15)</sup> In another study that was evaluating the use of visual-evoked potentials as a diagnostic tool for the assessment of any stage of HE, ten patients were diagnosed to have mHE. Two of these patients subsequently developed overt HE after a few weeks.<sup>(14)</sup> In the original study by Ridders et al which described the subclinical state of HE among cirrhotic patients with portal decompression surgery, three out of nine mHE patients developed episodes of overt HE within a year of follow-up.<sup>(13)</sup> Whether or not mHE truly predisposed them to the development of HE is not known, as portal decompression surgery itself is known to predispose one to the development of HE. Until recently, there had not been a study evaluating the natural progression of this condition in compensated early cirrhotics over a significant period of time. In 2001, a study was conducted on 63 cirrhotic patients (34 with mHE) who were followed up six-monthly till the development of overt HE, liver transplantation, death or till a maximum of four years.<sup>(2)</sup> In that study, either an abnormal number connection test or abnormal brainstem auditory evoked potential test was defined as indicating the presence of mHE. Of the patients with mHE, 46% had both tests abnormal while only 27% had an abnormal number connection test alone. By the end of the study, 19 patients had developed overt HE, 16 of whom had mHE at baseline. 18 of the 19 patients had obvious precipitants to their overt HE (e.g. upper digestive haemorrhage, spontaneous bacterial peritonitis). Three of the patients without mHE at baseline also had obvious precipitating factors for the development of their HE. However, the low number of events raised the possibility of a  $\beta$ -error. After developing an episode of overt HE, eight of the 19 patients died and four underwent liver transplantation. By multivariate analysis, the variables related to the development of HE included a low plasma glutamine level, the presence of oesophageal varices, degree of liver dysfunction and the existence of mHE. The study suggests that there is a strong association between the development of overt HE after the diagnosis of mHE in cirrhotics. If such a relationship truly exists, it would be imperative to screen for the presence of mHE, as

a first episode of acute HE is associated with a short survival of 23% at three years.<sup>(20)</sup>

In another study by Hartmann et al in 2000, they found that although patients with mHE more often had episodes of HE, survival was similar to that of patients without mHE. The study found that survival was determined mainly by the Child-Pugh score. Hence, the prognostic significance of mHE could be limited.<sup>(16)</sup> In a later study by Das et al, a follow-up of 20 patients with mHE and Child-Pugh score  $\leq 6$  found that five patients had 'recovered' from mHE. However, in their study, the presence of mHE was defined as at least two abnormal psychometric tests (hence reducing the sensitivity of detecting mHE) with psychometric testing repeated at 6–8 weekly intervals, which may have produced a partial learned response by the end of the follow-up period ( $5.4 \pm 1.3$  months).<sup>(21)</sup> In our study, we chose to re-evaluate our patients after three years in order to determine the progression or natural history of mHE over a longer period of time and in order to reduce the possibility of a learned response by patients. Choosing the time-interval to conduct a re-evaluation is entirely arbitrary; there is no gold standard, and other studies mentioned earlier have had varying interval periods between the tests. Perhaps we may have gained a better idea of the waxing and waning nature of mHE if we had tested the patients repeatedly within the three-year study period. However, our results showed that its absence after three years in previously-diagnosed patients already suggests a non-permanent nature of the disease.

Interestingly, our study showed that patients' QOL remained impaired despite the resolution or absence of mHE. While other authors have shown that mHE has a negative impact on a patient's QOL,<sup>(6,22)</sup> ours is the first study to show that this remains impaired even in its absence. A study by Groeneweg et al on 179 cirrhotic outpatients assessed QOL with the SIP. In this study, it was found that patients with mHE reported more impairment in their daily functioning. 36 of the 136 statements on the questionnaire were marked more often by patients with mHE. Further statistical analysis showed that five of these statements were predictive of the presence of mHE. In fact, with their study, the authors proposed a SHE probability scoring system to aid in the diagnosis of the condition, which included these five statements from the questionnaire.<sup>(18)</sup> However, with our new findings, we propose that perhaps QOL is less a function of mHE as it is of an underlying liver disease, as has been shown in other QOL studies comparing patients with underlying liver disease with the normal population.<sup>(23,24)</sup> Interestingly, QOL was also impaired in our patients who neither had mHE at baseline nor at the end of the study. The

second possibility is that QOL might be a function of time rather than mHE. Perhaps with time, as with any underlying chronic disease, patients' QOL is impaired, especially in the areas of social interaction (such as entertaining outside) and emotions (as with worrying about their illness). A third possibility for our results is the aetiology of cirrhosis. In our patients, the most common cause of cirrhosis was, by far, viral. This is in contrast to most of the western studies, where alcoholic cirrhosis made up a larger proportion of patients. This correlates with other studies which have shown that patients with viral hepatitis or liver disease tended to have poorer QOL than those with an alcohol aetiology.<sup>(25,26)</sup>

Our study has several limitations. Firstly, not all the patients consented to or could be recalled for a repeat evaluation. This could potentially introduce a bias to the study, as commonly, it is the more ill patients who tend to decline repeat evaluations or are lost to follow-up. There was no difference in age, gender, or aetiology of cirrhosis at baseline between the re-tested group of patients and those who were not (ie. those who did not consent to repeat evaluation, those lost to follow-up or those who had died). However, we accept that the patients who had died (who also had worse liver disease) may have continued to have mHE or even developed overt HE. Our second limitation was the lack of neurophysiological testing. However, although neurophysiological tests have been argued to be more specific in detecting mHE, psychometric tests are more sensitive.<sup>(3,15,27-29)</sup> We also specifically chose not to use neurophysiological tests for the purpose of patient convenience. This was a study conducted in the outpatient service and neuropsychometric tests have the advantage of being easily administered in a clinic setting and have high reproducibility. Thirdly, we did not control our data for the use of antiviral therapy in patients with chronic hepatitis. Although antivirals have never been studied specifically in mHE as a treatment for this specific entity, it is now established that antiviral therapy can stabilise and improve clinical cirrhosis. Hence, it would be intuitive to think that it may possibly be advantageous in mHE as well. Finally, our study excluded active alcohol users both at inclusion and subsequent recall, thus negating the effect of significant alcohol ingestion in our group of patients. However, it is not known if minimal alcohol may have played a role in test scores or the disease process (eg. patients who may have used alcohol minimally at baseline but chose to abstain completely during the study period might have different test or QOL scores). This has not been studied in mHE. We found no correlation between venous ammonia levels and the presence of mHE at baseline, as also shown in some other studies.<sup>(30)</sup> Hence, ammonia levels were not re-

evaluated at the time of follow-up testing three years later.

While we believe our study does not contradict previous studies suggesting that the presence of mHE predicts the development of overt HE, we question the value of a negative result for mHE at screening. If this condition is not static and does not necessarily progress from mHE to HE in a continuum, it begets the question of when would be the optimal time to screen such patients. In our study, we found the Child's score to be a predictor of mortality, regardless of the presence of mHE. Although there were limitations to our study, we believe that its results raise some pertinent questions with regard to the presumed natural history of mHE. Further studies with a larger cohort, diagnostic evaluation at closer intervals (e.g. conducted on an annual basis) and controlling for specific treatments employed for cirrhosis and its aetiologies, would probably be able to answer some of these questions. In conclusion, mHE may not be permanent and it may not necessarily be a harbinger of overt HE in the cirrhotic patient. The QOL remains impaired despite the resolution of mHE.

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