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CHRONIC LIVER DISEASES: EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT

# Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis

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**Abstract**

***Background and Aims***: The natural history of subclinical hepatic encephalopathy (SHE) is unknown. The present study was conducted to study the prevalence and the natural history of SHE in patients with cirrhosis of the liver.

***Methods***: One hundred and sixty-five patients with cirrhosis of the liver were studied. A total of nine psychometric tests (trail making and Wechsler adult intelligence scale-performance (WAIS-P) tests) were administered. Subclinical hepatic encephalopathy was present if two or more psychometric tests were abnormal. Seventy-two patients (SHE 40, without SHE 32) also underwent serial psychometric testing on follow-up visits at 6–8 week intervals.

***Results***: Subclinical hepatic encephalopathy was present in 103 (62.4%) patients. The number and figure connection, block design and picture completion tests were the most useful in the detection of SHE. Severity of SHE, as assessed by the number of abnormal tests, was greater in patients with more severe liver disease. During follow up, SHE tended to persist or worsen in patients with poorer liver function. Although other clinical complications were similar in different groups, overt hepatic encephalopathy developed more commonly in those patients who had SHE at entry compared to those who did not (22.6 *vs* 5.6%, $P=0.044$). Among the patients with SHE, the development of overt hepatic encephalopathy was more common in patients with Child's score of $>6$ than with Child's score of $\leq 6$ (40 *vs* 5%, $P=0.019$).

***Conclusions***: We conclude that SHE is common in cirrhosis. The natural history of SHE is worse in patients with advanced cirrhosis and SHE probably predisposes the cirrhotic patient to overt hepatic encephalopathy.



**Key words**: cirrhosis, hepatic encephalopathy, neuro-psychologic tests, psychometric tests, subclinical.

## INTRODUCTION

Neuro-psychiatric manifestations of chronic liver disease have varied features and incorporate not only the usual clinical stages of hepatic encephalopathy, but also a subclinical form. Subclinical hepatic encephalopathy (SHE) has been defined as 'a condition in which patients with cirrhosis, regardless of its etiology, demonstrate a number of quantifiable neuro-psychiatric defects, yet have a normal mental and neurologic status to clinical examination'.[1] In different studies using psychometric and electrophysiologic assessment, the prevalence of SHE among patients with cirrhosis has been found to range between 30 and 84%.[2–5] Although it is known that decreased performance ability may adversely affect the lifestyle of patients with SHE,[6,7] and that therapeutic measures such as dietary protein manipulation,[8,9] branched-chain amino acids,[10] administration of lactu-

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lose[11,12] or lactitol[13] result in an improvement in SHE, the natural history of SHE being largely unknown, the most practical treatment strategy for SHE has not been established. We therefore studied the prevalence and natural history of SHE over a period of time in patients with liver cirrhosis.

## METHODS

### Patients

One hundred and sixty-five liver cirrhotic patients were included in the present study. There were 139 males (aged 36.3 ± 8.4 years) and 26 females (aged 35.6 ± 10.9 years). The diagnosis of liver cirrhosis was based on clinical features and ultrasound findings or on histology. In these patients, the etiology of cirrhosis was alcohol in 41 (24.8%), hepatitis B virus (HBV) in 35 (21.2%) and non-alcohol and non-HBV in 89 (54%) patients. There were 41 (24.8%) patients in Child's A (Child's score ≤ 6), 72 (43.6%) in Child's B (score 7–9) and 52 (31.5%) in Child's C (score ≥ 10) grade. All patients were clinically stable and were not found to be in have hepatic encephalopathy after detailed neurologic and mental status examination.[14] None of the patients had a past history of overt hepatic encephalopathy or other neurologic or psychiatric disorders. No patient was taking drugs that were likely to interfere with psychometric performance, and none was abusing alcohol at the time of evaluation. Patients who had undergone shunt surgery for portal hypertension and patients with gastrointestinal (GI) bleeding within the preceding 6 weeks were excluded from the present study. Written informed consent was obtained from each patient participating in the present study.

In the latter half of the study, 72 patients also underwent serial psychometric testing along with regular clinical and laboratory evaluations on follow-up visits between 6 and 8 week intervals to document the natural history of SHE.

At entry, besides clinical examination, all patients were subjected to biochemical, ultrasound and endoscopic examinations, and Child's score was calculated for each patient. Ascitic fluid was examined for protein levels and white cell counts, and a polymorphonuclear leukocyte count of more than 250/mm$^3$ was taken as evidence of spontaneous bacterial peritonitis (SBP).[15]

### Psychometric evaluation

The diagnosis of SHE was made by quantitative psychometric tests that included the number connection tests (NCT) and figure connection tests (FCT) parts A and B,[4] and five performance subtests of Weschsler adult intelligence scale (WAIS-P) that is, block design (BD), digit symbol (DS), picture completion (PC), picture arrangement (PA) and object assembly (OA) tests.[16] The FCT was devised by us and is a universally applicable test for the assessment of mental state, which transcends the barriers of illiteracy and linguistic differences.[4] The clinical significance of these tests has been evaluated in a large number of healthy volunteers and patients with SHE.[4] Normal values were derived from 250 healthy volunteers, and the test score was considered abnormal if values were outside mean ± 2SD (Table 1). Different variations of NCT and FCT were used for serial evaluation to avoid any learning effect. Five tests of WAIS-P were administered according to a standard protocol described in detail previously.[4,16] These tests have been standardized for the Indian population. The test scores of all psychometric tests were corrected in all patients according to their educational status to rule out the effect of different levels of education.[4]

**Table 1** Prevalence of abnormal psychometric tests in 165 liver cirrhotic patients

| Psychometric tests | Normal values* | % Abnormal |
|---|---|---|
| Number connection test-A (s) | ≤ 40 | 44.8 |
| Number connection test-B (s) | ≤ 70 | 48.5 |
| Figure connection test-A (s) | ≤ 40 | 47.3 |
| Figure connection test-B (s) | ≤ 70 | 50.9 |
| Block design† | ≥ 10 | 41.8 |
| Picture completion† | ≥ 10 | 35.1 |
| Object assembly† | ≥ 10 | 32.1 |
| Digit symbol† | ≥ 10 | 31.5 |
| Picture arrangement† | ≥ 10 | 26.7 |

*Data obtained from 250 healthy volunteers,[4] †Scaled scores.

A total of nine psychometric tests (two trails each of NCT and FCT, and five WAIS-P tests) were administered to each patient, and the number of failed tests for each patient was noted. Subclinal hepatic encephalopathy was diagnosed if two or more psychometric tests were abnormal.[2–4,13]

All patients were followed up in the Liver Clinic (SGPGIMS, Lucknow) at 6–8 week intervals. At each follow-up visit, patients underwent clinical and biochemical assessments while serial psychometric testing was also conducted in the same manner in all 72 patients who were included in the latter part of the present study for studying the natural history of SHE.

Any patient with a clinical complication of cirrhosis, such as GI bleeding, hepatic encephalopathy, ascites etc., was treated according to standard protocol, on outpatient basis or after hospital admission, as warranted by the clinical condition. End-points for follow up included death, development of overt encephalopathy or completion of 6 months of follow up.

### Statistical analysis

Data were analyzed by using Fisher's exact test, Wilcoxon rank sum test and Kruskal–Wallis one way of

**Table 2** Clinical complications and follow up in patients with and without subclinical hepatic encephalopathy

| | SHE-A | SHE-B | NSHE-A | NSHE-B |
|---|---|---|---|---|
| Child's score | ≤6 | >6 | ≤6 | >6 |
| *n* | 20 | 20 | 14 | 18 |
| Complications | | | | |
| Ascites | 0 | 13 (65) | 0 | 14 (77.8) |
| SBP | 0 | 6 (30) | 0 | 6 (33.3) |
| Gastrointestinal bleed | 5 (25) | 9 (45) | 4 (28.6) | 8 (44.4) |
| Follow up | | | — | 2 (11.1) |
| Development of overt encephalopathy | 1 (5) | 8 (40)* | | |
| | 9 (22.5)† | | 2 (5.6)† | |
| Development of SHE | | | 1 (7.1) | 5 (27.8) |
| Deaths | 0 | 3 (15) | 0 | 2 (11.1) |

SBP, spontaneous bacterial peritonitis; SHE, subclinical hepatic encephalopathy; NSHE, no subclinical hepatic encephalopathy. Numbers in parentheses are percentages. * $P=0.01$; † $P=0.044$.

analysis where appropriate. A $P$ value $<0.05$ was taken as significant.

## RESULTS

Subclinical hepatic encephalopathy was present in 103 (62.4%) patients. The number of patients with abnormal tests was as follows: 74 (44.8%) NCT-A, 80 (48.5%) NCT-B, 78 (47.3%) FCT-A, 84 (50.9%) FCT-B, 69 (41.8%) BD, 58 (35.1%) PC, 53 (32.1%) OA, 52 (31.5%) DS and 44 (26.7%) PA.

Subclinical hepatic encephalopathy was equally frequent in patients with small (grades 1 and 2) and large (grades 3 and 4) esophageal varices (54.7 *vs* 68.8%, $P$=NS). The prevalence of SHE was similar in all Child's groups (56, 65.2 and 63.4% in Child's groups A, B and C, respectively, $P$=NS). However, the severity of SHE as determined by the number of abnormal psychometric tests was greater in patients with more severe liver disease. The mean number of abnormal psychometric tests was 2.95, 3.86 and 4.66 in Child's group A, B and C, respectively, and was significantly different among the three groups (groups A *vs* B $P<0.01$, B *vs* C $P<0.01$, and C *vs* A $P<0.001$). There was no difference in the frequency of SHE with respect to etiology of cirrhosis.

Of the 72 patients with liver cirrhosis who had serial psychometric evaluation, 34 (47.2%) were in Child's group A, 27 (37.5%) were in Child's group B and 11 (15.2%) were in Child's group C. Of these 72 patients, 40 patients had SHE at entry into the present study. They were further divided into two groups based on Child's score; 20 patients had Child's scores ≤6 (group SHE-A) and the other 20 patients had Child's scores >6 (group SHE-B). Similarly, of the 32 patients who had no SHE (NSHE) at entry, 14 patients had Child's score ≤6 (group NSHE-A) and 18 patients had Child's score >6 (group NSHE-B; Table 2). The mean (±SD) duration of follow up in these patients was 5.4±1.3 months and mean (±SD) number of follow-up psychometric assessments was 3.6±1.1.

Overt encephalopathy developed in nine of 40 (22.5%) patients with SHE at entry, while this developed in only two (5.6%) of 32 patients without SHE at entry ($P$=0.044; Table 2).

In group SHE-A, five of 20 (25%) patients had variceal hemorrhage requiring hospital admission and endoscopic sclerotherapy; only one patient developed overt hepatic encephalopathy following the GI bleed. Five patients recovered from SHE during the follow-up period while 14 patients continued to be in SHE. In these patients with persistent SHE, the number of abnormal psychometric tests worsened in one, improved in eight and was unchanged in the other five patients. In group SHE-B, 13 of 20 patients had ascites; seven patients needed hospital admission for control of ascites. Six patients had SBP while nine patients had GI bleeding. Six patients had both GI bleeding and SBP. A total of eight (40%) patients went on to develop overt encephalopathy, which was precipitated by a complication in all. In the absence of a precipitating factor, no patient had HE appear spontaneously. Of the 12 patients who were followed up until the end of the present study, none had fewer than two abnormal psychometric tests, while in five patients the number of abnormal psychometric tests increased.

During follow up, SHE tended to persist or worsen in patients with poorer liver function (i.e. group SHE-B). While five out of 20 patients in the SHE-A group recovered from SHE, none of the 20 patients in the SHE-B group recovered from SHE ($P$=0.024). Similarly, overt encephalopathy developed more commonly in patients in the SHE-B group than in the SHE-A group (5 *vs* 40%, $P$=0.019; Table 2).

In the NSHE-A group, four of 14 patients developed GI bleed while none had ascites. During follow up, psychometric evaluation showed development of SHE in

only one patient, who had repeated episodes of variceal bleeding. None of these patients developed overt encephalopathy. Among the 18 patients in the NSHE-B group, eight patients had GI bleeding requiring endoscopic sclerotherapy, 14 had ascites, six had SBP and five patients had both GI bleeding and SBP. Only two (11.1%) patients developed overt hepatic encephalopathy precipitated by GI bleeding and SBP. Follow-up psychometry revealed de novo development of SHE in five (27.8%) patients in the NSHE-B group, and one (7.1%) in the NSHE-A group ($P$=NS). Three patients in the SHE-B group and two patients in the NSHE-B group succumbed to their illness during follow up.

## DISCUSSION

The prevalence of SHE among patients with cirrhosis has been reported to be between 30 and 84%,[2–4] and our results corroborate this. As documented in a previous study,[2] the present study did not show any difference in the prevalence of SHE between patients with cirrhosis of different etiologies and between patients with different grades of esophageal varices.

Controversy exists in literature regarding the correlation between severity of liver disease and prevalence of SHE. Gilberstedt *et al.*[17] reported an impressive correlation between Child's score of severity of liver disease and WAIS-performance test scores, while Rikkers *et al.*,[9] Gitlin *et al.*[2] and Sood *et al.*[18] did not find any significant correlation between the severity of liver disease and the extent of psychometric test impairment. None of these studies attempted to assess objectively the severity of SHE, as defined by the number of abnormal psychometric tests. Although the prevalence of SHE in the present study was similar in different Child's groups, the numbers of abnormal psychometric tests were significantly different in the three Child's groups (C > B > A). This clearly implies that in cirrhosis the loss of performance skills because of SHE starts early in the disease and may progressively worsen with the progression of underlying liver disease and the worsening of hepatic function.

Overall, trail making tests (FCT and NCT) and block design tests were the most sensitive single tests, and the combination of NCT or FCT, block design and picture completion tests was the best combination for the detection of SHE.[4] Other studies also have found trail making, block design and digit symbol tests practical and easily administered tests to identify SHE.[2,17–19] As reported earlier, we found FCT to be very useful; and all patients could take this test irrespective of literacy and language barriers.[4] Two or more abnormal psychometric tests appears to be appropriate to diagnose SHE.[2–4,13] Also, none of the healthy subjects had two abnormal tests simultaneously.

It is not known if SHE evolves into the clinical stages of overt hepatic encephalopathy with the progression of underlying chronic liver disease and deterioration of hepatic function. The factors that determine the natural history of such a progression are also not understood. In an attempt to answer these questions, we followed up two groups of patients with cirrhosis with and without SHE over a period of 3–8 months to find out whether SHE persisted, resolved, appeared de novo or more importantly, evolved into overt encephalopathy. Over the follow-up period of $5.4 \pm 1.3$ months, we found that the liver function as assessed by the Child's score was the most important determinant of the natural history of SHE. Patients with better liver function had milder SHE, with fewer abnormal tests and tended either to recover from SHE or to have persistent SHE at the same level of severity, and only one (2.9%) of 34 went on to develop overt hepatic encephalopathy (Table 2). In contrast, patients with Child's score of six or more had more severe SHE, with a higher number of abnormal tests, and commonly (10 (26.3%) out of 38) developed overt hepatic encephalopathy, usually precipitated by a complication of liver cirrhosis (Table 2). Subclinical hepatic encephalopathy appears to be a useful indicator of liver function reserve. The likelihood of overt HE development appears to be related to the severity of underlying liver dysfunction. Those with more advanced liver dysfunction (SHE-B) are more likely to develop overt HE in the face of a clinical complication of cirrhosis like GI bleeding, ascites, SBP etc. than those with better liver function (SHE-A), while those with no SHE did not develop overt HE even in the face of such complications. Those patients who did not have SHE at entry had a similar frequency of clinical complications (depending on the severity of their liver disease) compared to those who had SHE, but interestingly, the frequency of overt encephalopathy was much less in this group. Therefore, it is interesting to know if treatment with lactulose or dietary modification prevents the development of overt encephalopathy in patients with liver cirrhosis and SHE on initial examination. The results of the present study indicate that SHE improved with 3 months of lactulose therapy in eight of 10 patients with SHE, while none of the 10 patients with SHE improved without lactulose therapy.[20] Two patients in the latter group also developed spontaneous overt encephalopathy.[20]

Few other long-term follow-up studies have been performed to document the natural history of SHE. In a recent study by Hartmann *et al.*,[21] patients with SHE significantly more often had episodes of overt hepatic encephalopathy than the patients without SHE. In the present study too, overt encephalopathy developed more commonly in patients who had SHE at entry than those who did not. In an uncontrolled study, three of nine cirrhotic patients with SHE developed overt hepatic encephalopathy during a 1 year follow-up period.[9] Yen and Liaw[22] have shown that 50% of 44 patients with decompensated liver cirrhosis developed overt hepatic encephalopathy during a follow up of 6 months. Significantly more patients with abnormal NCT-A or somatosensory evoked potentials at entry into the study developed overt hepatic encephalopathy (72%) than patients without these abnormal tests.[22]

The impact of SHE on survival in cirrhotic patients has not been studied extensively. While the present study and a study by Hartmann *et al.*[21] did not find any relationship between the presence of SHE and survival, Amodio *et al.*[23] did show a negative effect of SHE on the survival of these patients. They found that an

increased risk of death was associated with an altered Scan test or altered Choice 2 test.

A methodologic reservation about the present study could be that there are no data validating the use of performance tests in a serial longitudinal manner, and a 'learning effect' may adversely affect the results. To obviate the 'learning effect' in NCTs and FCTs, computer-generated variations of trails were randomly rotated during the administration of serial tests. The performance tests were administered at 6–8 week intervals and, in general, the results of these tests did not dissociate from those of the NCTs and FCTs, suggesting that a significant learning effect probably did not occur.

We conclude that: (i) SHE is frequent in patients with liver cirrhosis, appearing even in patients with Child's A liver function; (ii) its severity increases as liver function deteriorates, being most severe with Child's C liver function; and (iii) over the medium term (up to 6 months), it usually persists, although it may resolve or worsen with improvement or deterioration of liver function. Progression to overt HE is more frequent in patients with poorer liver function and is usually precipitated by clinical events such GI bleeding, SBP etc., while such progression is less likely in SHE patients with better liver function or without SHE. The spontaneous progression to overt HE, in the absence of a precipitating event was not noted in the present study, but may be noted over longer periods of follow up. The wide prevalence of SHE is likely to impact adversely on the quality of life of these patients and may warrant therapy on this account. The progression to overt HE may be best obviated by the prevention of, or prompt treatment of precipitating events, where possible. Long-term treatment of SHE may best be reserved for individuals with persistent severe SHE where no reversible factors are identifiable, especially if such therapy is shown to improve their quality of life.

## REFERENCES


1 Gitlin N. Subclinical portal-systemic encephalopathy. *Am. J. Gastroenterol.* 1988; **83**: 8–11.

2 Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy, ambulant, nonshunted patients with cirrhosis. *J. Hepatol.* 1986; **3**: 75–82.

3 Quero JC, Schalm S. Subclinical hepatic encephalopathy. *Semin. Liv. Dis.* 1996; **16**: 321–8.

4 Dhiman RK, Saraswat VA, Verma M, Naik SR. Figure connection test: a universal test for assessment of mental state. *J. Gastroenterol. Hepatol.* 1995; **10**: 14–23.

5 Yang S-S, Wu C-H, Chiang T-R, Chen D-S. Somatosensory evoked potentials in subclinical portosystemic encephalopathy: a comparison with psychometric tests. *Hepatology* 1998; **27**: 357–61.

6 Groeneweg M, Quero JC, De Bruijn I *et al.* Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998; **28**: 45–9.

7 Groeneweg M, Moerland W, Quero JC, Hop WC, Krabbe PF, Schalm SW. Screening of subclinical hepatic encephalopathy. *J. Hepatol.* 2000; **32**: 748–53.

8 De Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietary protein manipulations in subclinical portal-systemic encephalopathy. *Gut* 1983; **24**: 53–60.

9 Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy; detection, prevalence and relationship to nitrogen metabolism. *Gastroenterology* 1978; **75**: 462–9.

10 Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. *Gastroenterology* 1985; **88**: 887–95.

11 McClain CJ, Potter TJ, Kromhut JP, Zieve L. The effect of lactulose on psychomotor performance tests in alcoholic cirrhosis without overt hepatic encephalopathy. *J. Clin. Gastroenterol.* 1984; **6**: 325–9.

12 Watanabe A, Sakai T, Sato S *et al.* Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. *Hepatology* 1997; **26**: 1410–14.

13 Salerno F, Moser P, Maggi A, Vitaliani G, Benetti G. Effects of long term administration of low dose lactitol in patients with cirrhosis but without overt encephalopathy. *J. Hepatol.* 1994; **21**: 1092–6.

14 Parsons Smith W, Summerskill WHJ, Dawson AM, Sherlock S. The electroencephalogram in liver disease. *Lancet* 1957; **2**: 867–71.

15 Dhiman RK, Makharia G, Jain S, Chawla YK. Ascites and spontaneous bacterial peritonitis in fulminant hepatic failure. *Am. J. Gastroenterol.* 2000; **95**: 233–8.

16 Ramalingaswamy P. *Manual of Indian Adaptation of WAIS-Performance Scale*. Delhi: Manasayan, 1974; pp. 2–29.

17 Gilberstedt SJ, Gilberstedt H, Zieve L, Buegel B, Collier RO, McClain CJ. Psychomotor performance defects in cirrhotic patients without overt encephalopathy. *Arch. Intern. Med.* 1980; **140**: 519–21.

18 Sood GK, Sarin SK, Mahapatra J, Broor SL. Comparative efficacy of psychomotor tests in the detection of subclinical portal-systemic encephalopathy in nonalcoholic cirrhosis: search for a rational approach. *Am. J. Gastroenterol.* 1989; **84**: 156–9.

19 Tarter RE, Hegedus AM, Van Thiel DH, Schade RR, Gavaler JS, Starzl TE. Nonalcoholic cirrhosis associated with neuropsychological dysfunction in the absence of overt evidence of hepatic encephalopathy. *Gastroenterology* 1984; **86**: 1421–7.

20 Dhiman RK, Sawhney IMS, Chawla Y, Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. *Dig. Dis. Sci.* 2000; **45**: 1549–52.

21 Hartmann IJC, Groeneweg M, Quero JC, Beijema SJ, deMan RA, Hop WCJ, Schalm SW. The prognostic significance of subclinical hepatic encephalopathy. *Am. J. Gastroenterol.* 2000; **95**: 2029–34.

22 Yen CL, Liaw YF. Somatosensory evoked potentials and number connection test in the detection of subclinical hepatic encephalopathy. *Hepatogastroenterology* 1990; **37**: 332–4.

23 Amodio P, Del Piccolo F, Marchetti P *et al.* Clinical features and survival of cirrhotic patients with subclinical cognitive alterations detected by the number connection test and computerized psychometric tests. *Hepatology* 1999; **29**: 1662–7.