



RESEARCH ARTICLE

EVALUATION OF COGNITIVE DYSFUNCTION IN PATIENTS WITH LIVER CIRRHOSIS

*Dr. Sangeetha, K. P., Dr. Kumudha, P., Dr. Vishnu Priya, M. and Dr. Panneerselvam, T.

Department of Physiology, Govt. Mohan Kumaramangalam Medical College, Salem

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ABSTRACT

Introduction: The commonest complication of liver cirrhosis is hepatic encephalopathy. Hepatic encephalopathy is a complication of acute or chronic liver disease. Clinically hepatic encephalopathy can be classified as overt and Minimal. Minimal hepatic encephalopathy represents cognitive deficits in the absence of Overt encephalopathy.

Aims and Objectives: The study is conducted to evaluate cognitive dysfunction, which is a marker of subclinical or Minimal hepatic encephalopathy in liver cirrhotics by Minimal state examination and Number connection test.

Materials and Methods: 30 liver cirrhotics of both sexes in the age group 30 and 58 of various etiology with at least primary school education and without clinical evidence of hepatic encephalopathy were included in the study. Controls were age and sex matched healthy population. Both the controls and cirrhotics are subjected to MMSE, number connection test. Mean > 2 SD of controls was considered as cut off point for the diagnosis of minimal hepatic encephalopathy. The data were analysed by students 't' test.

Results: MMSE scoring showed no significant difference between both the groups. Controls were able to perform better in number connection test than cirrhotics (41.27 ± 11 vs 105 ± 49). About 63 % of cirrhotics had abnormal number connection test suggestive of cognitive impairment. No significant difference was observed in number connection test between alcoholic and nonalcoholic cirrhotics. Thus alcohol as independent factor in cognitive dysfunction can be ruled out.

Conclusion: Though all patients had preserved language, memory and verbal abilities there is significant cognitive impairment such as impaired attention and visuospatial orientation which may indicate minimal hepatic encephalopathy. This suggests the possibility that this disorder mainly affects prefrontal cortex and circuit between basal ganglia and prefrontal cortex. Thus periodic evaluation with number connection test may be helpful in diagnosing subclinical hepatic encephalopathy.

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INTRODUCTION

The relationship between the brain and the liver has been known for many years, ⁽¹⁾ and patients with chronic liver disease frequently experience neurological problems.⁽¹⁾ The commonest complication of liver cirrhosis is syndrome of hepatic encephalopathy. Hepatic encephalopathy is a complication of acute or chronic liver disease. Clinically hepatic encephalopathy can be classified as overt or minimal hepatic encephalopathy. Overt encephalopathy refers to neuropsychiatric abnormalities such as disorders of personality, altered level of consciousness, impairment of intellectual function, and neuromuscular dysfunction. It can be

diagnosed by bedside clinical examination and can be graded in severity according to West Haven criteria. By contrast minimal hepatic encephalopathy represents cognitive deficits in the absence of Overt encephalopathy. MHE patients have mild cognitive and psychomotor deficits. Subtle cognitive functions mainly affect attention, speed of information processing, motor abilities and coordination.⁽²⁾ Although termed "Minimal" diagnosis of this condition seems to be important for the following reasons :

- It has got negative impact on quality of life⁽⁶⁾ such as impairment of ability to drive due to visuospatial defect⁽⁶⁾
- It can predict the onset of Overt encephalopathy⁽⁷⁾.
- Psychomotor deficits could cause potential risk for patients working with heavy machineries.
- Condition is fully reversible with treatment⁽⁷⁾.

*Corresponding author: Dr. Sangeetha, K. P.

Department of Physiology, Govt. Mohan Kumaramangalam Medical College, Salem

- e. High prevalence rate. Prevalence varies from 30- 80%⁽²⁾. Prevalence ranges from 14% among Child Pugh class A to 45% in patients with Child Pugh class B/C⁽⁸⁾.
- f. As the number of cirrhosis patients is now increasing due to Hepatitis C virus and non alcoholic steatohepatitis, it is important to recognise the hepatic encephalopathy in its early stage and implicate treatment there by improving quality of life.⁽⁸²⁾

Because of high incidence of minimal hepatic encephalopathy and its negative impact on quality of life, routine early screening is recommended.

Prevalence of MHE

Varies from 22- 74% among cirrhotics. MHE is commonly diagnosed among cirrhotics, but patients with noncirrhotic portal hypertension.^(36,37,38) also shows some evidence of cognitive dysfunction

MHE and health related quality of life

Cognitive impairment in MHE affects attention, information processing, and psychomotor skills such as driving. Many daily activities such as dressing, shopping, and personal hygiene are not commonly affected. Blue collar workers with MHE are less likely to earn their daily wages compared to white collar workers with MHE. 60% of blue collar workers are unfit to work compared to 20% of white collar workers with MHE.

Aims and Objectives

To measure the cognitive dysfunction which is a marker of minimal hepatic encephalopathy, in a clinically normal cirrhotic patients by using psychometric tests such as MMSE, number connection test.

MATERIALS AND METHODS

Patients selection

Patients of both sexes in the age group between 30 and 58 diagnosed as cirrhosis without clinical evidence of encephalopathy were included in the study. They were selected from department of Hepatology, Rajiv Gandhi Government General Hospital, Chennai - 03. All the participants were informed about the study and a written and informed consent was obtained from them. Diagnosis of cirrhosis was based on clinical features, biochemical features, ultrasound finding and liver biopsy. Patients are classified according to severity of illness by Child Pugh's scoring as A, B, or C. Child Pugh scoring is based on 3 biochemical features such as bilirubin, albumin and prothombin values and 2 clinical features such as ascites and encephalopathy.

1 point assigned – (no encephalopathy, ascites – absent, bilirubin ≤ 2 mg/dl, albumin ≥ 3.5 gm /dl, prothrombin time ≤ 4 seconds)

2 points given if (encephalopathy is mild, ascites – mild, bilirubin 2.0 -3.0 mg/dl, Albumin 2.8-3.5gm/dl, prothrombin time – 4.0 - 6.0 sec)

3 points if encephalopathy severe , ascites –marked, bilirubin >3.0 mg /dl , albumin ≤ 2.8 gm/dl, prothrombin time > 6 sec. Each feature is assigned 1, 2 or 3 points.

Class A ; 5- 6 Points Class B; 7 -9 Points, Class C; 10-15 Points.⁽⁷⁸⁾

Detailed history including any neurological symptoms such as insomnia, confusion, memory loss, history of overt encephalopathy, are elicited. All the participants were subjected to thorough general and systemic examination. Any signs of liver cell failure such as spider naevi, caput medusae, gynecomastia, fetor hepaticus, and asterixis were noted

Inclusion criteria

Thirty patients with established liver cirrhosis of different etiology and Child Pugh classes without any overt neurological signs and symptoms at the time of testing.

Exclusion criteria

- * Patients with overt encephalopathy or history of overt encephalopathy
- * History of recent alcohol intake (within 3 month duration)
- * History of recent infection, antibiotic usage (within 6 weeks duration)
- * History of GI bleed (within 6 weeks duration)
- * Usage of drugs like benzodiazepines, antiepileptic drugs which affect psychometric performance
- * History of shunt surgery for portal hypertension
- * Patients with electrolyte imbalance
- * Patients with renal impairment
- * Presence of hepatocellular carcinoma
- * Medical disorders such as diabetes mellitus, hypertension
- * Any psychiatric illness
- * Hearing defects
- Visual defects
- * Illiteracy and inability to perform psychometric tests

Control group

Thirty age, sex, and education matched controls were selected from patients attending master health check up op of Rajiv Gandhi Government General Hospital after thorough history taking, clinical examination and laboratory tests.

Etiology of cirrhosis

Patients were considered to have alcohol etiology if daily intake of alcohol was more than 80g in men, 30 g in women for more than 5 years and testing negative for viral, and autoimmune etiologies were negative. Chronic hepatitis B and C diagnosis was based on HbsAG and Anti HCV viral markers. Autoimmune hepatitis was based on autoimmune markers such as antinuclear antibody, and smooth muscle antibody. Cryptogenic cirrhosis was diagnosed if extensive work up did not reveal any possible etiology

Minimental state examination

The Folstein Mini-Mental state examination is the most widely recognised and used bedside screening measure for global cognitive functioning. It consists of 30 points

- 5 – for orientation to time,
- 5 for orientation to place,
- 5 for attention,
- 3 for registration of 3 items,
- 3 for recall of 3 items after 5 minutes,
- 2 for naming objects,
- 1 for repeating phrase,
- 3 for following 3 stage command,
- 1 for printed command,
- 1 for writing a sentence and
- 1 for copying a diagram.

Orientation

Orientation to time and place is the most thoroughly addressed area, accounting for one third of the MMSE items, all other areas are assessed with fewer items. It provides information about subject's recent memory. Maximum score given was 10 points.

Registration

Subjects were told names of 3 objects and asked to repeat them. One point given for each correct answer. Immediate memory refers to the ability to keep a series of items under immediate attention such that they can be recited back.

Attention and calculation

The patients were asked to subtract 7 from 100 or to spell "world" backwards. These are immediate attention tests.

Recall

The short term memory is tested by including recall of the 3 unrelated words after 5 minutes. The Subjects were asked to repeat the words after presentation.

Language

Subjects were shown 3 common objects and asked to name them. One point was given for each correct answer. Subjects were asked to repeat a phrase of 4 or 5 words and One point was given if repeated correctly. Subjects were instructed to follow 3 stage command such as "take this paper in your right hand, fold it in half and put it on the floor" and one point for having performed correctly each stage. Subjects were asked to read and carry out simple commands written in a paper like "close your eyes" and one point was given if done correctly. Subjects were expected to write a sentence of their own choice and one point was given if written correctly.

Visual construction ability

Visual, spatial and construction abilities are all considered together as these functions are frequently affected in the right

parietal lobe lesions. Hence subjects were asked to copy pentagon figure from the MMSE and one point was given if drawn correctly.

Total score of MMSE is 30. Scores below 24 are indicative of cognitive impairment.

Number Connection Test (NCT)

It is a test of visuospatial orientation and psychomotor speed. The subject was given a sheet consisting of 25 numbered circles randomly spread over the sheet and asked to connect the numbers from 1 to 25 in order as quickly as possible. The time taken to complete the task including the time taken for correction of error was also noted⁽⁷⁹⁾. Lower the score, better was the performance. A cut off value greater than 2 S.D of the mean of controls is considered as abnormal.

RESULTS

Analysis was done by using statically packages for social sciences 16 software. For continuous data mean and standard deviation are computed and for discrete data proportion is computed. To compare the mean values between two groups, the independent t test is used for statically significance. To compare more than 2 groups means, the analysis of variance (ANOVA) was applied. All the statically significance is considered at 5% level.

Characteristics of study and control subjects

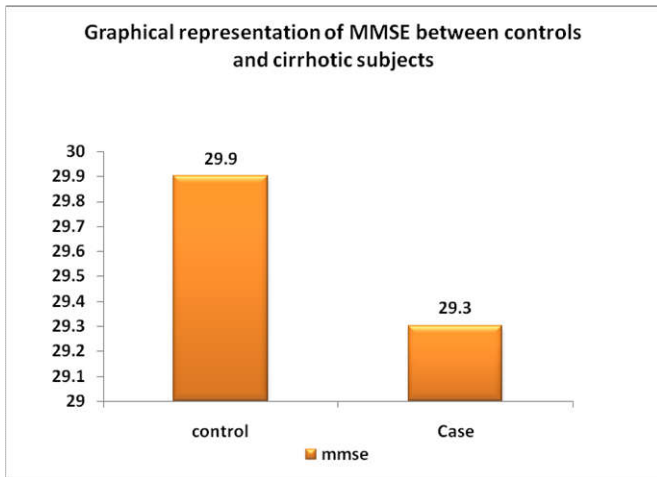
Our study population consists of 30 liver cirrhotic patients (20 males (60%) and 12 females (40%)) without clinical evidence of encephalopathy with age range from 22 -55 years. The control subjects were 30 in number with 12 females (40) and 20 males (60%) with the age ranging from 21-52 years. Their mean age was found to be 38.87 ± 9.187 in control group and the mean age of cirrhotic subjects was found to be 39.60 ± 8.865 . The duration of illness in cirrhotic patients varies from as low as 1.5 years to as high as 6 years. Regarding their literacy status, subjects among both groups at least have completed primary school education and were able to perform number connection test. Hence the distribution of study population among controls and cirrhotics were uniform according to age, gender and educational status. Considering the socioeconomic profiles of the study population most of the females were housewives, some are employed in hostels, departmental stores, textile industry and few were involved in agricultural work. Some of the males were found to be working in tea shops, shoe company, others involved in driving, security job, tailoring and agricultural work. On classifying the cirrhotic subjects according to etiology 18 were found to be of alcohol induced cirrhosis and remaining 12 were found to be non alcohol related cirrhosis due to Hepatitis B virus, hepatitis C virus and cryptogenic cirrhosis. Based on the severity of illness it was found that out of 30 cirrhotic patients, 24 patients belong to Child-Pugh's A class with a score of 5-6 points and 6 patients belong to Child Pugh class B with a score of 7-9 points. The ophthalmological examination including visual acuity, colour vision, field of vision were normal except for refractory errors which have been corrected by glasses.

Minimental state examination

No significant difference was observed in minimental state examination score in both the study group of controls and cirrhotics. The average score in the controls was found to be 29.9 ± 0.3 and the mean score among the cirrhotic subjects was found to be 29.3± 0.45.

Table 1. Comparison of MMSE scores among cirrhotics and control subjects

Study Group	Mean	Standard deviation	P value
Control	29.9	0.305	0.072
Cirrhotics	29.3	0.45	



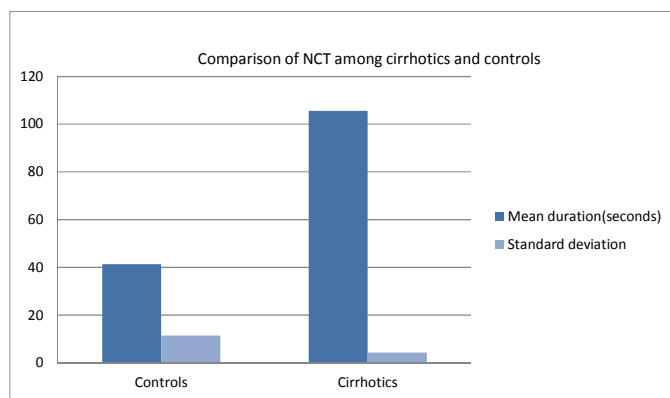
Number Connection tests

In the performance of the number connection tests it was observed that controls were able to perform better compared to cirrhotics.

Table 2. Comparison of number connection test scoring among cirrhotics and control

Study Group	Mean Duration	Standard Deviation	P value
Controls	41.27	11.46	
Cirrhotics	105.57	49.59	0.000**

** p value < 0.01 denotes highly significant value.



The controls were able to complete the test with the mean duration of 41.27 ± 11.46 seconds compared to cirrhotics whose average duration was found to be 105.57 ± 49.59

seconds. Considering the etiology, the average duration of test was higher in alcoholic group with the mean of 110.39 ± 57.95 and in the non alcoholic group the mean duration of test was found to be 98.33± 34.62. Though the mean duration was higher in alcoholic group it was not statically significant. p value < 0.05 was considered to be statically significant.

Table 3. Comparison of number connection test scoring among cirrhotics of alcoholic and nonalcoholic etiology

Study group	Mean duration	Standard deviation	pvalue
Alcoholic cirrhotics	110.39	57.95	0.524
Non alcoholic cirrhotics	98.33	34.61	

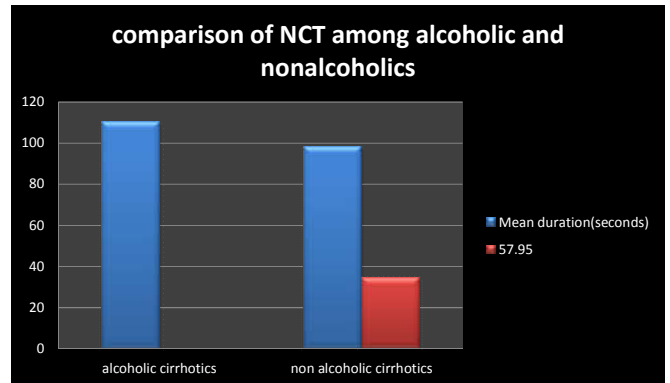


Table 4. Frequency of abnormality in number connection test (Mean + 2 Sd of controls)

	Frequency	percent	Valid percent	Cumulative percent
Valid	19	63.3	63.3	63.3
Abnormal	11	36.7	36.7	100
Normal	30	100.0	100.0	
Total				

According to Portal hepatic encephalopathy index scoring number connection test performance greater than 30 seconds is taken as impaired performance. But none of our control subjects are not able to complete the number connection test within 30 seconds. So we applied the cut off point mean > 2 SD of controls, (64.2 seconds), to find out the percentage of abnormality. It was observed that 19 cirrhotics (63%) showed abnormal performance of number connection test.

DISCUSSION

All the cirrhotic patients included in the present study had normal neurological examination which is in accordance with definition of minimal hepatic encephalopathy given by the working party at the 11th world congress of gastroenterology. It defines minimal hepatic encephalopathy as presence of measurable cognitive deficits in liver disease patients and /or with portal systemic shunting that are not identified by detailed clinical history or clinical examination, but are detected by abnormalities in psychometric tests and neurophysiological variables in the absence of other known cause of abnormal cognitive tests. In this study diagnosis of minimal hepatic encephalopathy was made by the abnormality in psychometric test (number connection test > 2 S.D) In the

present study age, sex, education, were comparable among both the groups of cirrhotics and controls. Cirrhosis was due to alcohol etiology among 60% patients and 40% due to non alcoholic etiology such as hepatitis B and C, cryptogenic, autoimmune.

MMSE scoring

There was no significant difference noted between cirrhotics and control groups in MMSE scoring suggesting that none of the patients suffered from gross cognitive impairment. Scoring less than 24 was taken as cut off point for the diagnosis of cognitive impairment. Normal finding in MMSE rules out the presence of clinically overt encephalopathy. The present study is similar to study by Juan quero *et al* who showed normal mental status assessment by MMSE despite their abnormalities in other psychometric test. Like wise the present study is consistent with the study by Tombaugh *et al* (90) in 1996 who has stated that MMSE has limited ability to detect subclinical cognitive impairment. According to study by Diman *et al*, Bajaj J.S *et al* MMSE must be employed as screening test before applying diagnostic tests for MHE. Further the Study by Almin H (7) showed 15 % abnormality in MMSE scoring among cirrhotics compared to control population which was different from the present study. This difference may be attributed to difference in the study population. The patients enrolled in their study were of Child Pugh B and C and none of the patients belong to Child Pugh A class. But in the present study 80% of the patients belong to Child Pugh class A and only 20% belong to class B and none of the patients belong to class C.

Number connection test

In the number connection tests the mean duration of the performance of cirrhotics was significantly higher compared to controls. (41.26 ± 11 vs 105.57 ± 49). Mean > 2 SD of controls was considered as cut off point for the diagnosis of minimal hepatic encephalopathy. About 19 patients (63%) of cirrhotics showed abnormal scoring in number connection test based on the cut off value. This is in accordance with the study by Prasad S *et al*, Das A *et al*, Sharma *et al* Gitlin *et al* who employed similar scoring for number connection test. This abnormality represent subtle cognitive deficits such as attention, visuospatial orientation and motor speed defects which may indicate presence of minimal hepatic encephalopathy. Though the mean duration of performance of number connection test in alcoholics was higher compared to nonalcoholics, it was not statistically significant. Both alcoholics and nonalcoholics have cognitive dysfunction attributed to alteration in metabolic function of liver due to cirrhosis and alteration in neurotransmission. Hence the alcohol as an independent factor in causation of cognitive dysfunction cannot be considered. It is only the presence of liver failure which leads to metabolic disturbance and altered neurotransmission. Alcohol may be an additional factor in cognitive impairment. Likewise Edwin *et al*. (93) studied cognitive impairment in alcoholics and nonalcoholics and found that they were equivalent in tests of learning, memory, simple and complex attention and general intellectual ability. Also the study performed by Juan Quero *et al* in liver

cirrhotics without encephalopathy showed 50% abnormal scoring in number connection test. Moreover studies by Ciecho mickaiska in 22 liver cirrhotics without encephalopathy showed that there was no significant difference in the performance of number connection test between cirrhotics and controls. (49.5 ± 7.5 vs 45.3 ± 17.5). Study by Praveen sharma *et al* 2010 in 200 liver cirrhotics showed 48% of cirrhotics had abnormal number connection scoring compared to controls which was lower percentage compared to present study. This low percentage of scoring in their study may be attributed to difference in the level of education in study population. In their study, 18 % of them were graduates with 15 years of formal education degree holders and 80% were under graduated with 12 years of formal education. In our study most of the patients had only about 5- 7 years of formal education and none of the patients were degree holders. The present study was almost similar to study by Zeegen *et al* who observed 60% abnormality in number connection test in patients who have undergone portal systemic shunt surgery even though they had normal mental status on clinical examination. They also suggested that impairment in the performance of star construction test was less common than impairment of number connection test.

The difference in abnormality observed by many authors may be due to difference in study population, severity of illness or level of education status and the different cut off points used by different authors. According to Mc Crea in 1996, the patients with cirrhotics have impaired attention even though they do not have language, memory or constructive abnormality. Also Posner and Peterson 1990 have suggested that impaired attention was due to reduction in the function of anterior attention system. Further studies by Amodio *et al*. 1995 and Mc Crea *et al*., 1996 have shown that impaired attention was due to reduction in activation of reticular – cortical activation or cortico – reticular –cortical influences. The present study was also in accordance with the above mentioned studies where all patients had preserved language, memory and verbal abilities as evidenced by normal MMSE scores with impaired attention and visuospatial orientation. This suggests the possibility that this disorder mainly affects prefrontal cortex and circuit between basal ganglia and prefrontal cortex.

Conclusion

Both the cirrhotics and control group had similar scoring in MMSE. There is significant cognitive impairment among cirrhotics even though there was no clinical evidence of encephalopathy is proved beyond doubt as evidenced by impaired psychometric test. Minimal state examination was not found to be a sensitive test for detecting subtle cognitive deficits. Prevalence of minimal hepatic encephalopathy increases with increase in severity of illness as shown by 100% prevalence in Child Pugh class B compared to 50% in Child Pugh class A. Cognitive performance in control group was significantly higher compared to cirrhotics (41.26 ± 11 vs 105.57 ± 49) by number connection test. About 63% of cirrhotics showed abnormal number connection test scoring. Thus the subtle cognitive deficits which cannot be shown by MMSE can be detected by other psychometric test such as number connection test.

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