"STUDY OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS OF LIVER"

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ENDORSEMENT

This is to certify that the dissertation entitled **STUDY OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS OF LIVER** is a bonafide research work done by **REG. NO. BG0114015.**

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LIST OF ABBREVIATIONS

MHE:	-	Minimal Hepatic Encephalopathy.
HE:	-	Hepatic Encephalopathy.
SHE:	-	Subclinical Hepatic Encephalopathy.
WCOG:	-	World Congress Of Gastroenterology.
NCT-A:	-	Number Connection Test - A.
NCT-B:	-	Number Connection Test - B.
DST:	-	Digit Symbol Test.
MELD:	-	Model For End Stage Liver Disease.
PSS:	-	Portosystemic Shunting.
PSE:	-	Portosystemic Encephalopathy.
OHE:	-	Overt Hepatic Encephalopathy.
TIPSS:	-	Transjugular Intrahepatic Portosystemic Shunting.
CHE:	-	Covert Hepatic Encephalopathy.
GABA:	-	Gamma-Amino Butyric Acid.
PET:	-	Positron Emission Tomography.
DSM-IV:	-	Diagnostic Statistics And Manual IV.
ISHEN:	-	International Society For Hepatic Encephalopathy And Nitrogen Metabolism.
DTR:	-	Deep Tendon Reflex.
HM:	-	Hepatic Myelopathy.
BCAA:	-	Branched Chain Amino Acids.
AAA:	-	Aromatic Amino Acids.
EEG:	-	Electroencephalography.
WAIS-R:	-	Wechsler Adult Intelligence Scale – Revised.

WAIS:	-	Wechsler Adult Intelligence Scale.
MRS:	-	Magnetic Resonance Spectroscopy.
HRQOL:	-	Health Related Quality Of Life.
SIP:	-	Sickness Impact Profile.
HBV:	-	Hepatitis B Virus.
HCV:	-	Hepatitis C Virus.
mg/dl:	-	Milligram/Decilitre.
gm/dl:	-	Gram/Deciltre.
µL:	-	Microlitre.
PT:	-	Prothrombin Time.
INR:	-	International Normalized Ratio.
g/dL:	-	Gram/Deciliter.
USG:	-	Ultrasonogram.
n:	-	Number.

ABSTRACT

Introduction: Minimal hepatic encephalopathy (MHE) affects 30-80% of the patients with cirrhosis, and it is suggested that despite no recognizable clinical symptoms of neurological abnormalities it may cause cognitive deficits. The aim of our study was to diagnose the patients of MHE in cirrhosis of liver patients without any overt signs of neurological abnormalities.

Methodology: Patients with liver cirrhosis were selected independent of the etiology of the disease. Detailed history and clinical examination was done. Psychometric tests were applied to evaluate the presence of MHE in the form of NCT-A (number connection test-A) and DST (digit symbol test). Test scores were compared with the normal values of corresponding age group normal values.

Results: 100 patients were included with a mean age of 49.24 years. Prevalence of MHE was 54% (n = 54). Significant deterioration in the test scores corresponding to Child-Pugh class and MELD score was also observed.

Conclusion: The presence of MHE in apparently normal individuals is confirmed by our results. This also shows the need to screen all apparently normal cirrhotic patients with such tests.

Key words: Cirrhosis of liver, Psychometric tests, Minimal hepatic encephalopathy.

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INTRODUCTION

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[1]

Hepatic encephalopathy (HE) is a frequent complication and one of the most debilitating manifestations of hepatic disease, affecting the lives of the patients and the caregivers. Along with it, cognitive impairment associated with liver cirrhosis results in utilization of more health care resources in adults than any other manifestation of liver diseases.[2]

The neuropsychological features of HE were described long ago. Hippocrates mentioning "those who are mad on account of phlegm are quiet, but those on account of bile are vociferous, vicious, and do not keep quiet".[5] The first comprehensive study of neuropsychiatric manifestations of HE was done by Sherlock et al in 1954 where they described the clinical presentation of 18 patients with liver disease and neurological signs and symptoms.[6]

Traditionally HE is graded into four stages of severity, ranging from abnormal behavior to coma.[3] In addition, a subclinical stage has been described, in which patients of cirrhosis show a number of quantifiable neuropsychological defects, yet have a normal mental and neurological status on global clinical examination.[4] This subclinical stage started to come into light since 1970s when several studies showed that many liver cirrhosis patients without clinical signs of encephalopathy (normal conventional neurological and mental assessment) fared significantly worse in psychometric tests as compared to healthy controls.[5] They were initially labeled as

suffering from 'latent' or 'subclinical' HE for which the recent term 'minimal hepatic encephalopathy' (MHE) is used[7] according to the recommendation of Working Party at the 11th World Congress of Gastroenterology, 1998.[14] The prevalence of this subclinical hepatic encephalopathy (SHE) has been reported to vary from 30% to 84%, depending on the tests and population used.[8]

It is suggested that MHE affects patients' daily activities, work performance and quality of life, as well as increase the risk of falls and causing and/or suffering traffic accidents. Several studies have shown that patients with MHE are unfit to drive a car.[11] Patients with minimal hepatic encephalopathy exhibit significant impairment in car handling, adaptation and cautiousness as well as in several driving actions, such as following road signals, paying attention towards pedestrians and cyclists, checking rearview mirror before changing lanes, tracking, signaling before turning and following traffic rules.[12] MHE may also predict development of overt hepatic encephalopathy (OHE) and poor prognosis.[9] Additionally, MHE patients also have impaired attention span and impaired ability to sleep. Still the controversy around the consistency in the effect of MHE on quality of life persists.[10]

Despite the high prevalence of MHE in liver cirrhosis patients as shown in various studies controversy still exists regarding the testing of MHE which is confounded by various factors like age, geography, educational level. There are certain neurophysiological tests available too for diagnosis but because of the cost involved psychometric tests are preferred. Currently there are 5 psychometric tests available as components of psychometric hepatic encephalopathy score – digit symbol test (DST), number connection test – A (NCT – A), number connection test – B (NCT – B), serial dotting and line drawing.13 These tests are inexpensive and easy to perform. The Working Party recommended use of at least two or more psychometric

tests for diagnosing MHE.[13] Few studies have also shown the diagnostic value of brainstem auditory evoked, somatosensory evoked potentials, EEG, critical flicker frequency for testing but these are cumbersome and expensive.[14,15]

The cognitive impairment in MHE is characterised by impairment in attention, response inhibition, visuo-motor coordination, and working memory. These skills are affected in MHE and hence the consequent deficit in psychometric tests.[16]

Small intestinal bacterial overgrowth is higher in patients with MHE as compared to the patients without MHE. Pathogenesis of MHE is believed to be same as that of overt HE with ammonia playing a key role. These patients have higher level of ammonia and low plasma albumin but bilirubin levels are not significantly different than the patients without MHE.[17]

The importance of diagnosing MHE lies in the fact that this stage of encephalopathy may be fully reversible with treatment.[18]

The main therapeutic intervention of benefit in this setting is lactulose (4-O-β-d-galactopyranosyl-d-fructose) which is aimed at reducing ammonia level. Lactulose decreases the colonic pH as a result of the production of organic acids by bacterial fermentation which creates an environment that is both hostile to the survival of urease-producing gut flora, such as Klebsiella species and Proteus species, and advantageous to the growth of acid resistant, non-urease producing species, such as lactobacilli and bifidobacteria, resulting in reduced production of ammonia in the colonic lumen. In addition, acidification of colonic secretions reduces the absorption of ammonia by nonionic diffusion.[19]

Increase in blood-brain barrier permeability to ammonia, cerebral metabolic rate for ammonia, and cerebral glutamine/glutamate signaling on magnetic resonance

spectroscopy have each been documented.[19,20] Ammonia induced alterations in cerebral blood flow and glucose metabolism have also been described.[21]

Therapeutic intervention at this stage leads to improvement in cognitive functions translating into improvement in quality of life (which can be assessed by using health related quality of life –HRQOL questionnaires, Sickness Impact Profile – SIP questionnaires).[22]

The present study aims to identify and study the patients of MHE in liver cirrhosis so as to help them give early diagnosis and treatment and also to avoid progression to encephalopathy and complications related to cognitive impairment such as driving which might lead to accidents.

OBJECTIVES

1. To diagnose minimal hepatic encephalopathy in patients with cirrhosis of liver.

REVIEW OF LITERATURE

Advanced liver disease and portosystemic shunting (PSS), are not an isolated disorder of the liver, rather they have well known consequences on the body and, notably, on brain functioning.[23] The alteration of brain functioning, which can produce behavioural, cognitive, and motor effects, were termed portosystemic encephalopathy (PSE)[6] and later included in the term HE.[24] Unless underlying liver disease is successfully treated, hepatic encephalopathy (HE) is associated with poor survival and a high risk of recurrence.[25] Even in the mildest form (MHE) reduces quality of life and is a risk factor for bouts of severe HE.[26]

Definition of HE

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[1] This definition is based on the concept that encephalopathies are “diffuse disturbances of brain function”[25] and the adjective “hepatic” implies causal connection to liver insufficiency and/or perihepatic vascular shunting.[27]

Hence we can say that hepatic encephalopathy refers to a wide spectrum of neuropsychiatric abnormalities that occur in patients with acute or chronic liver disease. Many a times, the term used is "porto-systemic encephalopathy" which emphasises the failure of the liver to detoxify toxins that escape from the intestine. These toxins bypass the liver entering into the systemic circulation, and cause primary or secondary changes in brain neurochemistry which produces symptoms of hepatic encephalopathy. This

metabolic disorder is characterized by reversibility suggesting a lack of persistent structural lesions in the brain.[34]

The incidence and prevalence of HE are related to severity of the underlying liver insufficiency and PSS.[28] In patients with cirrhosis, overt HE (OHE) is an event that defines the decompensated phase of the disease, such as variceal bleed or ascites.[26] Overt hepatic encephalopathy is also reported among subjects without cirrhosis with extensive PSS.[29]

Manifestation of HE may not be obvious on clinical examination and there are multiple tools used for its detection, which may influence the variation in the reported incidence and prevalence rates. The prevalence of OHE at time of diagnosis of cirrhosis is 10%-14% in general[30], 16%-21% in those with decompensated cirrhosis,[31] and 10%-30% in patients with transjugular intrahepatic portosystemic shunt (TIPSS).[32] The cumulated numbers indicate that OHE will present in 30%-40% of those with cirrhosis at some time during their clinical course and in survivors in most cases repeatedly. Minimal HE (MHE) or covert HE (CHE) occurs in 20%-80% of patients with cirrhosis.[33] The true incidence and prevalence of OHE in patients is difficult to establish, because of considerable heterogeneity in etiology and disease severity. The lack of a gold standard for assessing the presence of hepatic encephalopathy means that the incidence of more minor forms (MHE) is difficult to ascertain.[35] It is unlikely for a single mechanism to cause the whole spectrum of hepatic encephalopathy in its various forms; a multifactorial pathogenesis looks much more likely. Current thinking says that a combination of chronic low-grade glial edema along with potentiation of the effects of gamma amino butyric acid (GABA) on central nervous system by ammonia may be responsible for many symptoms of hepatic encephalopathy.[36] Neuropathologically, hepatic encephalopathy is

characterised by astrocytic rather than neuronal change. In fulminant hepatic failure where hepatic encephalopathy develops within 4 weeks of onset of liver disease, autopsy reveals brain edema and astrocytic swelling. In patients with cirrhosis and porto-systemic shunts, typical finding is the Alzheimer type II astrocyte (i.e., enlarged astrocytes containing prominent nucleoli, margination of chromatin, and a large, pale nuclei), which is pathological hallmark of hepatic encephalopathy. They are found in multiple locations, including cortex and the lenticular, lateral thalamic, dentate and red nuclei.[37] These abnormal astrocytes have been shown to be produced because of ammonia. Above said findings are similar to those in acquired hepatocerebral degeneration syndrome. Positron emission tomography (PET) shows significantly decreased glucose utilization in cerebral cortex and concomitant increased utilization in thalamus, caudate lobe, and cerebellum. These findings suggest that decreased metabolism in the brain of patients with chronic liver disease might explain the neuropsychiatric abnormalities which are characteristic of hepatic encephalopathy. The outlook for patients who develop overt hepatic encephalopathy is poor. After the first episode of overt hepatic encephalopathy, the 1year survival is about 40%, falling to approximately 15% after 3 years.[39] Study by Bustamante et al showed similar mortality rates, despite the improvements in intensive medical care that has occurred over the intervening 20 years.[40] Hepatic encephalopathy continues to be major clinical problem. In subjects having acute liver failure, a patient can succumb to neurological death, with brain edema and intracranial hypertension.[41] In patients with cirrhosis the Child-Pugh classification recognizes the prognostic significance of HE.[42] A multi axial definition of HE is hence required that defines both the type of hepatic abnormality and the duration and the characteristics of neurological manifestations in chronic liver disease.

Classification of HE[1]

Hepatic encephalopathy should be classified according to all of the following four factors[13] :

1. According to the underlying disease, HE is subdivided into

• Type A resulting from acute liver failure.

• Type B resulting predominantly from portosystemic bypass or shunting.

• Type C resulting from cirrhosis.

The clinical manifestations of types B and C are similar, whereas type A has distinct features and, notably, may be associated with increased intracranial pressure and a risk of cerebral herniation.

2. According to the severity of manifestations. The continuum that is HE is arbitrarily subdivided (Table 1).

WHC INCLUDING MHE	ISHEN	DESCRIPTION	SUGGESTED OPERATIVE CRITERIA	COMMENT
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible
All conditions are required to be related to liver insufficiency and/or PSS.				

Table 1: Classification of hepatic encephalopathy.[1]

3. According to its time course, HE is subdivided into

• Episodic HE: In the DMS-IV classification system, it corresponds to a "Delirium due to a General Medical Condition."

• Recurrent HE denotes bouts of HE occurring with a time interval of 6 month or less.

•Persistent HE denotes pattern of behavioural alterations that are present and interspersed with relapses of overt HE. This includes cognitive defects which impact negatively on social and occupational functioning. Persistent non-cognitive abnormalities (such as extra pyramidal alteration or sleep disturbance) require separate tabulation. It is subdivided into mild (HE grade 1) and severe (HE grades 2-4), according to degree of impairment of autonomy, and treatment dependent persistent encephalopathy (overt symptoms develop promptly after discontinuing medication).

4. According to existence of precipitating factors, HE is subdivided into

• Nonprecipitated.

• Precipitated.

The precipitating factors have to be specified. Precipitating factors can be identified in almost all bouts of episodic HE type C and should be actively sought after and treated when found (Table 2).

EPISODIC	RECURRENT
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Modified from Strauss E, da Costa MF. The importance of bacterial infections as precipitating factors of chronic hepatic encephalopathy in cirrhosis. Hepatogastroenterology 1998;45:900-904.
**More recent unpublished case series confirm the dominant role of infections.*

Table 2: Precipitating factors of hepatic encephalopathy.[1]

Minimal HE: The Working Party recognized the widespread use of term "subclinical encephalopathy," but changed it to "minimal hepatic encephalopathy." In contrast to patients with symptomatic encephalopathy, patients having minimal HE have no recognizable clinical symptoms of brain dysfunction. Hence, the prerequisite for diagnosing Minimal HE is the careful exclusion of clinical symptoms.

CLINICAL PRESENTATION

Hepatic encephalopathy produces wide spectrum of nonspecific neurological and psychiatric manifestations.[43] In its mildest form, HE alters only psychometric tests oriented toward attention, working memory, psychomotor speed, and visuo-spatial ability, electrophysiological and other functional brain measures.[44] As HE advances, personality changes like apathy, irritability, and disinhibition, might be reported, and alterations in consciousness and motor function occur. Disturbance of the sleep-wake cycle with excessive daytime sleepiness are frequent,[45] whereas complete reversal of sleep-wake cycle is less consistently observed.[46] Patients may develop progressive disorientation towards time and space, inappropriate behaviour, along with acute confusional state with agitation or somnolence, stupor, and, coma.[47] ISHEN

(International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus uses onset of disorientation or asterixis as the onset of OHE.[48]

In noncomatose patients with HE, motor system abnormalities such as hypertonia, hyper-reflexia, and positive Babinski sign, may be observed. In contrast, deep tendon reflexes (DTRs) may diminish and even disappear in coma,[49] although pyramidal signs may still be observed. Rarely, transient focal neurological deficits may occur.[50] Seizures may occur very rarely in HE.[51] Extrapyramidal dysfunction (e.g., hypomimia, muscular rigidity, bradykinesia, monotony and slowness of speech, Parkinson's like tremor, and dyskinesia with diminished voluntary movements) are common findings; whereas, the presence of involuntary movements similar to tics or chorea happen rarely.[49] Asterixis or "flapping tremor" is often present in early to middle stages of HE which precede stupor or coma and is, in fact, not a tremor, rather a negative myoclonus consisting of loss of postural tone. It is very easily elicited by actions that require postural tone, e.g., hyperextension of the wrists with separated fingers or rhythmic squeezing of the examiner's fingers. Asterixis may be observed in other areas, such as feet, legs, arms, and eyelids. Asterixis is not pathognomonic of HE as it may be observed in other diseases (e.g., uremia).[52]

The mental and motor signs of HE might not be expressed, or do not progress in parallel, in all the individuals, hence producing difficulty in staging the severity of HE.

Hepatic myelopathy (HM)[53] is a particular pattern of HE probably related to marked, long standing portocaval shunting, which is characterized by severe motor abnormalities exceeding mental dysfunction.

Persistent HE may present as prominent extrapyramidal and/or pyramidal disturbance, partially overlapping with HM, in which postmortem brain examination may

reveal brain atrophy.[54] This condition was previously termed as acquired hepatolenticular degeneration, a term not used currently. However, this cirrhosis associated Parkinsonism is usually unresponsive to ammonia lowering therapy and may be seen more commonly than originally thought in patients having advanced liver disease, presenting in around 4% of cases.[55]

It is widely accepted in clinical practice that all forms of HE along with their manifestations are completely reversible, and this assumption is still a well founded basis for treatment strategies. However, research on post liver transplant HE patients and on patients after resolution of repeated attacks of OHE casts doubt on full reversibility. Some mental deficits may persist.[56] Similarly, episodes of OHE may be associated with persistent deficits in working memory and learning.[57]

Pathogenesis of Hepatic Encephalopathy

The various models of pathogenesis of hepatic encephalopathy are based on the data derived from experimental animal models, brain tissue from in vitro studies, magnetic resonance spectroscopy and PET. Our understanding of this condition is incomplete because of difficulties of studying brain function in vivo such as poor accessibility, inability to topographically map the areas of brain associated with alertness. In general, all hypotheses concentrate on changes in brain energy levels, metabolic abnormalities in the structure and functioning of neuronal and synaptic membranes, and alterations in the neurotransmitter function. Understanding of the pathogenesis of hepatic encephalopathy is based on the following three postulates:

1. The causative metabolites/toxins (usually nitrogenous substances) most likely originate in intestine.

2. Because of porto-systemic shunts, these toxic substances bypass liver, where they are normally metabolized.

3. After bypassing the liver, these toxic metabolites cross the blood-brain barrier and exert their direct or indirect neurotoxic effects on central nervous system.

The pathogenesis of hepatic encephalopathy is thought to be multifactorial. Several processes are implicated to have a causative role:

1. Accumulation of toxins in the brain

The first experiment indicating a nitrogenous substance as the cause of hepatic encephalopathy was performed by Eck, a Russian physiologist who made porto-systemic shunts in healthy dogs and observed that the dogs promptly became comatose after having meat. Role of ammonia has been postulated on the following basis:

• A reproducible increase in the blood ammonia level of patients with cirrhosis.

• The development of hepatic coma in patients having advanced liver disease and in the experimental animals after ingesting ammonia,

• Elevated serum ammonia level in the children having genetic abnormalities of urea cycle synthesis, which is associated with neuropsychiatric changes which are similar to those of patients having hepatic encephalopathy,

• Increased cerebral metabolism of ammonia,

• Increased permeability of blood-brain barrier to ammonia, and chronic elevation of blood ammonia level, which leads to characteristic changes in the astrocytes.[58]

The lack of strong correlation between blood ammonia level and the stage of hepatic encephalopathy has been used as an argument for that ammonia may not be the only contributing factor in the pathogenesis. However, not all the data is consistent with ammonia toxicity theory. Poor correlation of ammonia level with hepatic encephalopathy,

the presence of this condition even in the absence of elevated ammonia level, and neuroexcitatory effects of low ammonia level all cast a doubt on the theory.[59] Other toxins have also been shown to play a role in the pathogenesis. Patients with chronic liver disease have raised blood levels of short-chain fatty acids (such as butyrate, valerate) which may cause neuroinhibition. Likewise, there is an increase in serum mercaptans which are formed by colonic bacteria from methionine. Mercaptans result in fetor hepaticus in the patients with cirrhosis. A synergistic effect of these toxins has been proposed by Zieve and Colleagues[60] as a working hypothesis emphasizing the action of ammonia.

2. False neurotransmitters

Patients with cirrhosis are found to have a decreased ratio of branched-chain amino acids (BCAA) to aromatic amino acids (AAA), from 3.5:1 to 1:1. It is postulated that the increase in AAA in central nervous system may interfere with physiologic neurotransmission by competitively inhibiting normal neurotransmitters (such as dopamine, norepinephrine) and favouring formation of weak, false neurotransmitters (such as octopamine). This hypothesis raises the possibility that correction of the BCAA:AAA ratio might lead to improvement of hepatic encephalopathy. However, several clinical trials have failed to demonstrate that the changes in the ratio through intravenous or oral administration of BCAA result in any clinical significant improvement of this condition.[61]

3. Accumulation of neuroinhibitory substances

During the 1980s, Basile and Jones[62] at National Institutes of Health promoted gamma-amino butyric acid (GABA) (the major inhibitory neurotransmitter in central nervous system) as a cause of hepatic encephalopathy. These authors suggested that the raised ammonia levels enhance the GABA-ergic neurotransmission and hence synergistically augment the action of benzodiazepine receptor agonists. This unifying hypothesis led to the consideration of another synergistic process as an explanation for HE.

4. Accumulation of manganese

Potential role of the manganese in the pathogenesis of hepatic encephalopathy is based on the finding that more than 80% of patients having cirrhosis in hepatic coma are found to have increased concentrations of manganese. It is proposed that ammonia and manganese act synergistically. It is not clear as of yet if manganese accumulation in brain is an epiphenomenon or whether there exists a cause and effect relationship.[63]

5. Monoamines

Many of the early neurological symptoms of hepatic encephalopathy (such as altered sleep pattern) have been attributed to modification of monoamine neurotransmitter serotonin. Serotonin is derived from amino acid tryptophan, uptake of which is facilitated by elevated serum ammonia level. Elevated cerebrospinal fluid concentration of L-tryptophan and serotonin metabolites has been observed in the brain of patients with hepatic encephalopathy. Level of the serotonin-degrading enzyme mono-amine oxidase is also increased in the brain of patients having cirrhosis suggesting serotonin synaptic deficits.[64]

6. Endogenous opiates

Abnormalities of endogenous opioid system in patients having hepatic encephalopathy are suggested by the increased sensitivity to morphine, increased plasma level of the endogenous opioid met-enkephalin, as well as the increased concentration of beta-endorphins in the brain extract of rats with porto-caval shunts.[65]

Differential diagnosis

The diagnosis requires the detection of signs which are suggestive of HE in patients with severe liver insufficiency and/or PSS who do not have any obvious alternative causes of brain dysfunction. The recognition of precipitating factors causing HE (such as infection, bleeding, and constipation) supports the diagnosis of hepatic encephalopathy. The differential diagnosis should consider common disorders which alter the level of consciousness (Table 3).[1]

Overt HE or acute confusional state
Diabetic (hypoglycaemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Other presentations
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea
Hyponatremia and sepsis can both produce encephalopathy per se and precipitate HE by interactions with the pathophysiological mechanisms. In end-stage liver disease, uremic encephalopathy and HE may overlap.

Table 3: Differential diagnosis for hepatic encephalopathy.[1]

Diagnosis of Hepatic Encephalopathy

The diagnosis of hepatic encephalopathy is according to careful neuropsychiatric evaluation. Neurological findings in patients having cirrhosis of liver and hepatic encephalopathy are usually confined to the mental and motor status. Evidence for disordered mental status might be evident while recording history. Emphasis is to be placed on attentiveness by the examiner and evidence of some subtle changes in daily living, such as decrease in energy level, disturbance of sleep pattern, and impairment of cognition, consciousness, or any motor function. Neurological diseases like subdural haematoma, Wernicke's disease, encephalitis, metabolic abnormalities (e.g., electrolyte disturbances, renal dysfunction), drug intoxications (e.g., alcohol, narcotics, sedatives) should be ruled out.

Episodic Encephalopathy

West Haven criteria is frequently used to grade HE from grade I to IV which is based on changes in consciousness, intellectual function, and behaviour. Glasgow coma scale which measures response to eye opening, verbal behaviour, and motor responsiveness tells about neurological impairment and is less prone to observer variability than evaluation of consciousness.[26] In studies of overt manifestations of HE, both the grading systems have their place.

Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behaviour Impaired performance of subtraction
Grade 3	Somnolence to semi stupor, but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Table 4: West Haven grading of hepatic encephalopathy.

Persistent Encephalopathy

In 1977, Conn[67] introduced a scoring scale, the PSE index which was subsequently used in many clinical trials. It combined mental state with arterial ammonia level, degree of asterixis, electroencephalographic (EEG) findings and the result of number connection test (NCT). Initially NCT was developed to test organic brain damage in alcoholic patients and later was adapted to be used to quantify HE. In episodic encephalopathy, the PSE index has not proved to be superior to clinical grading. Its shortcomings limit its use for quantifying HE in clinical studies of encephalopathy. Psychometric tests require adjustment to demographic and cultural confounding variables.[68] Arterial ammonia level is more accurate than venous level, but still correlates poorly with the symptoms of HE.[69]

Minimal Hepatic encephalopathy

The problem of diagnosing minimal HE is dual[70]

1. Semantic.

2. Factual.

At semantic level, a label was originally applied to a population of individuals performing abnormally on psychometric tests who presented as essentially normal on clinical neuropsychiatric examination. This observation merely shows that psychometric tests are more sensitive as compared to observational methods, a finding which is frequently observed in other neuropsychiatric disorders with dementia. With the advances in neuroimaging methods and more powerful methods for analysing electrical activity of brain, it appears that psychometric tests are not unique and may even be less sensitive in identifying impairment in persons who appear normal on clinical examination.

At factual level, this could be explained by two possible explanations. In the first, minimal encephalopathy may be a different entity from either episodic or persistent encephalopathy, with distinct pathogenesis. Alternatively, the neuropsychiatric disorder encompassing both clinical and subclinical variants can be quantitatively and qualitatively characterised according to the symptom profile at different levels of severity. In this scenario, these two entities can be hybridised into one common syndrome having qualitatively distinctive features according to the severity. To summarise, introduction of term "subclinical" has led to confusion because its definition depends on the use of measurements beyond ordinary reach of clinicians, contributing to an opinion that minimal encephalopathy is a specific disorder. Whereas this possibility may exist but it yet has to be demonstrated empirically. Alternative challenge is to determine clinical dimensions, best measurement procedures, and a scoring algorithm which can validly diagnose hepatic encephalopathy throughout the spectrum of its severity.[71]

Neuropsychological tests

Neuropsychological tests are being used for the diagnosis of hepatic encephalopathy for more than 40 years. It was in fifties that measurements like construction or reproduction of a five pointed star or handwriting started being used for the diagnosis of HE. Although all these tests were able to depict an increase or decrease in the constructional ability of a patient but it was extremely difficult to quantify the test result. Hence in the seventies psychometric tests which could be evaluated quantitatively not only qualitatively were introduced for the diagnosis of hepatic encephalopathy. In general, psychometric tests have to have the following characteristics - they have to be objective, reliable, valid and sensitive. It is desirable to have such a psychometric test which could produce specific results in distinct diseases but practically this cannot be

expected with the present tests available. Neuropsychologists have designed a lot of tests that try to fit into the criteria listed above. Most of these tests have been applied to patients with HE. However, independent studies of these tests found some interesting results. While the verbal ability of the patients was unchanged they did worse than healthy controls in the tests of motor speed and accuracy, visual perception, visuospatial orientation, visual construction, concentration, attention and memory. Hence, the psychometric test batteries which are to be used for the diagnosis of SHE ought to identify exactly these defects in the field of cognition. Unfortunately, until today there is no agreement as to which tests should be used in practice, although there is an obvious need to find an agreement to find a basis for the comparability of therapeutically studies. Testing across neuropsychological domains should be the preferred approach[72] in identifying selective abnormalities in areas like attention and fine motor function. In only very few instances the influence of age, sex, education, and other cultural differences on the result of these tests has been systematically evaluated in patients with liver disease. However, the need for shorter evaluation has led to the use of four tests in most clinical studies: Number connection test (NCT-A and NCT-B), digit symbol test, and block design test. The block design and digit symbol tests are part of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). A standardised test battery including the NCT-A and B, the line tracing test, the serial dotting test, and the digit symbol test (PSE syndrome test) has a high specificity for HE as compared with other metabolic encephalopathy.[73]

Neurophysiologic tests

Both, the EEG and evoked potentials, may be used for the detection of MHE. Because of more sophisticated technical requirements for evoked potential studies the EEG has been used predominantly. Major findings include a general decrease in wave frequency and an increase in wave amplitude. First, the theta waves with a frequency between 4 - 7 Hz occur, and then these theta waves predominate and are supplanted by delta waves with a frequency of 1 - 3 Hz. In addition there is preterminal loss of wave amplitude and flattening of the curve. These abnormalities are not restricted to overt encephalopathy but may be found even in cirrhotic patients without any clinical sign of encephalopathy. It must be emphasized, however, there is no close correlation between grade of HE and the degree of EEG abnormalities.[74] As compared to the psychometric tests, the sensitivity of EEG for the diagnosis of MHE is limited. EEG is useful in follow-up examinations. Clinical improvement in patients with HE is often found to be preceded by an increase in EEG frequency, while on the other hand a future HE episode may be predicted by the decrease in EEG frequency of a patient. This is true even if a patient with an individual frequency of 12 Hz for example presents with a 9 or 8 Hz EEG, which according to the definition is within the normal range but is undoubtedly pathological as compared to his/her individual standard frequency.[74] Changes in the EEG or evoked responses are nonspecific and do not allow for the diagnosis of HE. Simplest EEG assessment in HE is to grade the degree of abnormality of conventional tracing. A more refined assessment can be obtained with the help of computer assisted techniques of analysis including the mean dominant EEG frequency and the power of a particular rhythm.[75] Among the most sensitive tests of evoked potentials is the P300 peak obtained in the auditory oddball paradigm.[76] Major difficulty in validating neuropsychological

and/or neurophysiologic testing is the lack of a precise definition of what constitutes the "gold standard" for MHE.

Other tests

The PSE index has been used for studying MHE. Its usefulness in this setting is not been prospectively validated. Recently, a quality-of-life questionnaire (sickness impact profile) is being used to detect the extent and frequency of deficits in daily functioning in patients with cirrhosis without clinically apparent HE. Impairment of both the physical and functional functioning was noted in patients with abnormal neuropsychological and/or neurophysiologic testing.

Consensus Statement

For Episodic or Persistent Encephalopathy, clinical grading of the abnormal mental state should be used for quantifying purpose. Stages I-IV include changes in consciousness, intellectual function and behaviour. Glasgow coma scale is useful for patients in stages III and IV. For MHE, at least two of the following psychometric tests should be used: NCT-A, NCT-B, block design test, digit-symbol test. A standardized test battery including NCT A and B, line tracing test, serial dotting test, and digit symbol test is recommended.

Neurophysiologic tests (such as EEG with mean dominant frequency, P300 auditory evoked potentials) should be used wherever possible. In the exchange between Sir Toby Belch and Sir Andrew Aguecheek in Shakespeare's Twelfth night, we hear a reference to the effects of alcohol on the brain, and quite possibly to hepatic encephalopathy precipitated by dietary protein.[77]

According to US National Institute of Diabetes and Digestive and Kidney Diseases, approximately 25000 Americans die from cirrhosis of the liver each year, making it the seventh leading cause of death by disease. The cost to the society from cirrhosis, in the form of direct medical care, and lost and diminished productivity is substantial. A significant number of these patients develop hepatic encephalopathy and require admission to the hospital for treatment. Prompt diagnosis of hepatic encephalopathy usually poses few problems for experienced clinicians. Comparatively, the evaluation and diagnosis of a more subtle cerebral dysfunction in the patients without overt evidence for hepatic encephalopathy is much more complicated.

Reports of cerebral dysfunction in few patients with cirrhosis who had no evidence of overt hepatic encephalopathy as revealed by standard neurological examinations began to appear about two decades ago, the first of which was reported by Rikkers et al[78] who found unsuspected electroencephalogram abnormalities which were consistent with hepatic encephalopathy in 33% of patients and abnormal performance on the Trail making test in 60% of the patients with portocaval shunt. They chose the term 'subclinical' to describe these patients. The term subclinical hepatic encephalopathy gained widespread acceptance.

Studies of such patients have centred on patients with normal neurological examination. Unlike neuropsychological tests, a substantial portion of the standard neurological examination is subjective in nature and is therefore difficult to standardize and use in a comparative manner. To overcome these limitations, substantial effort has been made to develop standards, such as Unified Parkinson's Disease Rating Scale, for examination of select group of patients with specific neurological problems. Similar efforts have not been made to evaluate the clinical and neurological status of patients

with cirrhosis. To complicate the issue further, these examinations are often conducted by non-neurologists or by the persons without any special training and expertise in the diagnosis and evaluation of such patients. Therefore, although the literature may indicate that such patients are normal according to the usual clinical criteria, it is possible that very subtle deficits may have eluded detection in patients with cirrhosis of liver. Rikkers and his colleagues[78] identified that the incidence of subtle hepatic encephalopathy ranged from 10 to 50% in patients with portocaval shunts. As the usual scales for the evaluation of HE used gross clinical indicators, they sought evidence for more subtle cerebral dysfunction by using a variety of neuropsychological tests, including the Wechsler Adult Intelligence Scale (WAIS), Reitan Trail making test A and B, Williams visual memory test, simple reaction time to light and sound, and choice reaction time to light and sound. The patients whom they studied all had portocaval shunts for 1 - 5 years and were unimpaired as assessed by using the usual clinical rating scales. Control individuals were matched for age, sex, and education. They found that seven out of the 10 test scores were worse in the patients than control individuals by t tests. The Trail making test A and B were most frequently abnormal (in 60 and 53%, respectively). Significant correlations were found between the fasting venous blood ammonia level and performance on four neuropsychological tests (Trail making B, Williams visual memory, simple reaction time to light, and complex reaction time to sound), suggesting that ammonia caused the above said abnormalities. Subsequently, there have been more such studies that have confirmed these initial observations in cirrhotics caused by various etiologies. Schomerus et al[79] evaluated 40 patients with chronic liver disease and portal hypertension. 15 had cirrhosis due to alcohol and 15 had cirrhosis because of other causes. Patients with alcohol-induced pancreatitis who were matched to the patients on the basis of age, sex, and

alcohol consumption were used as control. The authors commented specifically on the capacity to drive. 60% were found unfit to drive, with an additional 25% classified as marginally fit. All of the 15% who were considered fit to drive were non-alcoholic. Virtually all the patients with EEG changes were unfit to drive, even if the EEG abnormalities were minor. They referred to this syndrome as 'latent portosystemic encephalopathy'. In a similar study of 37 biopsy proven cirrhotic individuals with apparent normal neurological examinations, Gitlin et al[80] found that 70% failed two or more neuropsychological tests. They found that the Trail making test, digit symbol test and block design test of the WAIS were the most sensitive measures. Tarter et al[81] have shown that cirrhosis has impact on daily life which is out of proportion to the apparent severity of the illness. In their study, they used the sickness impact profile and compared 30 patients having non-alcoholic cirrhosis with 18 patients having Crohn's disease as control to study the effects of chronic disease. They found that sleep, rest, body care, movement, physical dysfunction, and recreation and pastime scales on the sickness impact profile showed evidence of more marked impairment in the cirrhotic individuals. A recent study by Cordoba and others[82] confirmed the high prevalence of sleep disorders in liver cirrhosis patients. They found that 47.7% of the cirrhotic patients compared with 4.5% of the control individuals reported unsatisfactory sleep. They also showed that disturbed sleep was associated with higher indices of depression and anxiety. To determine whether the etiology of cirrhosis affected cerebral function, Tarter and his friends tested four groups of patients. To compensate for the effects of disease, investigators again used patients with Crohn's disease as the control population.[83] Their battery contained 24 separate measures. They tested 3 different populations with cirrhosis: those with cirrhosis secondary to alcohol, those with cirrhosis secondary to

hepatocellular disease, and those with cirrhosis secondary to biliary tract disease (primary biliary cirrhosis and primary sclerosing cholangitis). They found out that cirrhosis secondary to alcohol group failed 37% of the tests, the hepatocellular disease cirrhosis group failed 32%, and the primary biliary cirrhosis and primary sclerosing cholangitis group failed 20%, whereas the Crohn's disease group failed the least at 18%. Among the various test categories, cirrhosis due to alcohol group failed over 60% of the tests of perceptual/motor ability. All the three groups of cirrhotic persons performed at a level which was significantly worse than that of the control group on the same scale. Same was true for tests of attention, although cirrhosis due to alcohol group, again the most severely affected, failed approximately 30% of the tests. Tests of learning and memory were abnormal only in cirrhosis due to alcohol group. As the results of language tests were similar in all groups and because some cognitive domains were more severely affected than others, the cognitive impairment associated with cirrhosis appears to be selective rather than global in nature. These findings include slight tremors and equivocal changes in muscle tone in absence of asterixis or extensor plantar signs.

Hence, there is a general agreement among various studies in the literature that a battery consisting of the Trail making test A and B, digit symbol test, and block design test of the WAIS, augmented by the Purdue or grooved pegboard test, is more likely to detect subtle neurological deficits in this population.

Although neurophysiologists categorize these tests into a variety of sets related to the cognitive domain being emphasized (e.g. attention and concentration, perceptual, motor, spatial and language), successful completion of all these tests requires a sustained focused mental effort. A variety of studies have shown that anterior cingulate gyrus plays a central role in attention demanding tasks.[84] Studies of cerebral glucose metabolism have

shown that there is a reduction in the glucose metabolism of anterior cingulate gyrus in such patients.[85] A deficit in the function of anterior attention system may underlie the manifestations of mild forms of hepatic encephalopathy.

Many of the reports about subtle deficits in cirrhotic persons have shown that such patients improve with specific treatment. Rikkers et al[78] reported improvement after a reduction in dietary protein, whereas few others have shown that lactulose and lactitol are effective. A recent study of 13 cirrhotic persons with abnormal performance on number connection test, digit symbol test, and block design test[86] showed that lactulose (45ml/day for 8 weeks) contributed to the resolution of deficits in half of the patients as compared to persistence of the deficits in 85% of those not treated. There exist several dilemmas surrounding the patients with cirrhosis without any evidence of overt hepatic encephalopathy. The first of these centres on deciding which is the best way to monitor the patients at risk of developing HE. It is important to recognize that, in spite of what may appear to be a patient with normal cerebral function, it is likely that a mild or minimal degree of encephalopathy is present and that even mild encephalopathy is having significant impact on daily life. Like many patients with subtle chronic problems with an insidious onset, these patients and their families are unaware of the fact that they are impaired. In many cases, the encephalopathy may be reversed after treatment. Hence, all the patients with cirrhosis or unequivocal signs of severe liver disease should be screened for evidence of mild cognitive impairment. Until the results of a large prospective study are available, it would be prudent to ask specifically about the activities of daily living, specifically sleep wake cycles and recreational activities at each clinic visit. Historical evidence for disturbed sleep and withdrawal from the society may herald onset of encephalopathy. Patients should also be screened with a brief battery of

neuropsychological tests as mentioned above. Care is to be taken to ensure that these tests are administered and scoring done exactly as specified.

Quero et al[87] have shown that failure to use age appropriate normative values for such tests results in an over-diagnosis or under-diagnosis of cerebral dysfunction hence rendering the test useless. Neuroimaging tests are not likely to be helpful unless the history or examination suggests the presence of an acquired structural lesion of brain.[88] Electrophysiological tests may be used, but require special equipment and trained personnel.[89] Until more sensitive and specific methods are developed to determine whether a cirrhotic patient has mild encephalopathy, the diagnosis and decision to treat has be made on clinical criteria alone. As the benefits of improved cognitive function may be substantial while the risks associated with the use of lactulose are small, periodic empiric clinical trials are warranted for many patients with cirrhosis of liver.

Minimal hepatic encephalopathy is the present term that has replaced the old terms of latent or subclinical hepatic encephalopathy. It was felt that these older terms did not reflect the importance of this syndrome in patients' lives. The pathogenesis of minimal hepatic encephalopathy is poorly understood. It would seem likely that the same mechanisms affecting neurotransmission in overt hepatic encephalopathy also underlie minimal hepatic encephalopathy. There is no reason to think that hepatic encephalopathy is all or nothing phenomenon, and a continuous scale of impairment seems more likely.[90] Alteration in the pattern of cerebral blood flow has been demonstrated in the patients with minimal hepatic encephalopathy, and it seems likely that this also plays a role in its pathogenesis. As the syndrome of minimal hepatic encephalopathy has only recently been defined, its clinical characteristics are poorly described.

Kircheis et al[91] suggested that using the technique of critical flicker frequency may be effective in identifying cases of minimal hepatic encephalopathy. This is a promising technique, and may help in screening patients who may then need more formal neuropsychological assessment. Neuroimaging techniques like magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have been used in assessment of minimal hepatic encephalopathy, but at present they are more being used in research and to further establish the pathophysiology of this condition.[92]

How these patients should be treated remains uncertain. Studies have shown an improvement in cognitive functioning with dietary protein restriction or lactulose treatment. If there is a scale defining neurological and cognitive dysfunction with minimal hepatic encephalopathy at one end of the spectrum and overt hepatic encephalopathy at the other, it would seem reasonable that similar treatments would work in each condition.

The prognosis of minimal hepatic encephalopathy has recently been studied, and 30% of patients who showed signs of minimal hepatic encephalopathy went on to develop overt hepatic encephalopathy. Unfortunately, in this study the authors did not make it clear over what period this occurred, as they followed patients until one of three end-points occurred (death, transplantation or overt hepatic encephalopathy). The mean time taken for developing hepatic encephalopathy was about 2 years from the initial assessment. Other studies have also indicated that minimal hepatic encephalopathy is an independent predictor of poor survival in patients with liver disease. These findings are not in consistence with another study which showed that the presence of minimal hepatic encephalopathy was of limited prognostic significance.[93] In this study however, patients having MHE had more episodes of overt HE, and as we know that overt hepatic

encephalopathy is associated with poor prognosis,hence, it could be postulated that the author's negative findings simply reflect a lack of long-term follow-up.

METHODOLOGY

Source of data: Patients admitted in KLE'S Dr PRABHAKAR KORE HOSPITAL and MEDICAL RESEARCH CENTRE, Belagavi.

Study design: A cross-sectional study.

Sample size: 100.

Study period: The study is being conducted from January 2015 to December 2015.

Sampling procedure:

Based on the following formula sample size of 100 patients was considered:

Sample size calculation: $4pq/d^2$

40% prevalence.

10% absolute error.

Inclusion criteria:

1) Patients with cirrhosis of liver.

Exclusion criteria:

1) Age<18 years.
2) Metabolic encephalopathies.
3) Cerebrovascular accident.
4) Pre-existing neurological disorders.
5) With history of lactulose intake.
6) Poor vision.

Ethical clearance:

Prior to the beginning, the study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College Belagavi (Annexure – I).

Informed Consent:

The patients who fulfilled the selection criteria were informed about the nature of study and a written informed consent was obtained (Annexure-II).

Method of collection of data

Patients admitted with cirrhosis of liver were subjected to detailed history, examination and processed through necessary investigations with informed consent. Following investigations were done:

- Complete haemogram.
- Liver function tests.
- Renal function tests.
- HCV/ HBsAg.
- Ultrasonogram abdomen.

Following two tests were used to diagnose minimal hepatic encephalopathy:

NUMBER CONNECTION TEST – A: The subject is shown a sheet of paper with 25 numbered circles which are randomly spread over the paper. The task is to connect the circles from 1-25 as quick as possible. Test result is the time needed by the subject including error correction time.

DIGIT SYMBOL TEST: The subject is given a series of double-boxes with a number given in the upper part. The task is to draw a symbol pertinent to this number into

the lower part of the boxes. Nine fixed pairs of numbers and symbols are given at the top of the test sheet. Test result is the number of boxes correctly filled within 90 seconds.

According to the normative parameters for NCT-A and DST established by Bao et al,[94] for Asian population diagnostic criteria for MHE are as follows: time greater than two SD from the mean for the NCT, and score less than two SD from the mean for the DST. For the NCT-A, diagnostic criteria are: > 34.3 sec in patients aged < 35 years; > 45.7 sec in patients aged 35-44 years; > 52.8 sec in patients aged 45-54 years and > 61.9 sec in patients aged > 55 years. Diagnostic criteria for the DST are: < 40.5 in patients < 35 years; < 35 in patients aged 35-44 years; < 28.5 in patients aged 45-54 years and < 26 in patients aged > 55 years. Patients with abnormal results from both psychometric tests were diagnosed as having MHE.

Data so collected with respect to various parameters was entered in the proforma (Annexure-III) and analysis was done.

Statistical methods

The data obtained was entered into the Microsoft excel spreadsheet (annexure-IV). The categorical data was expressed in terms of rates, ratios and percentages and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation and comparison was done using independent‘t’ test. A Probability value (p-value) of less than or equal to 0.05 was considered as statistically significant.

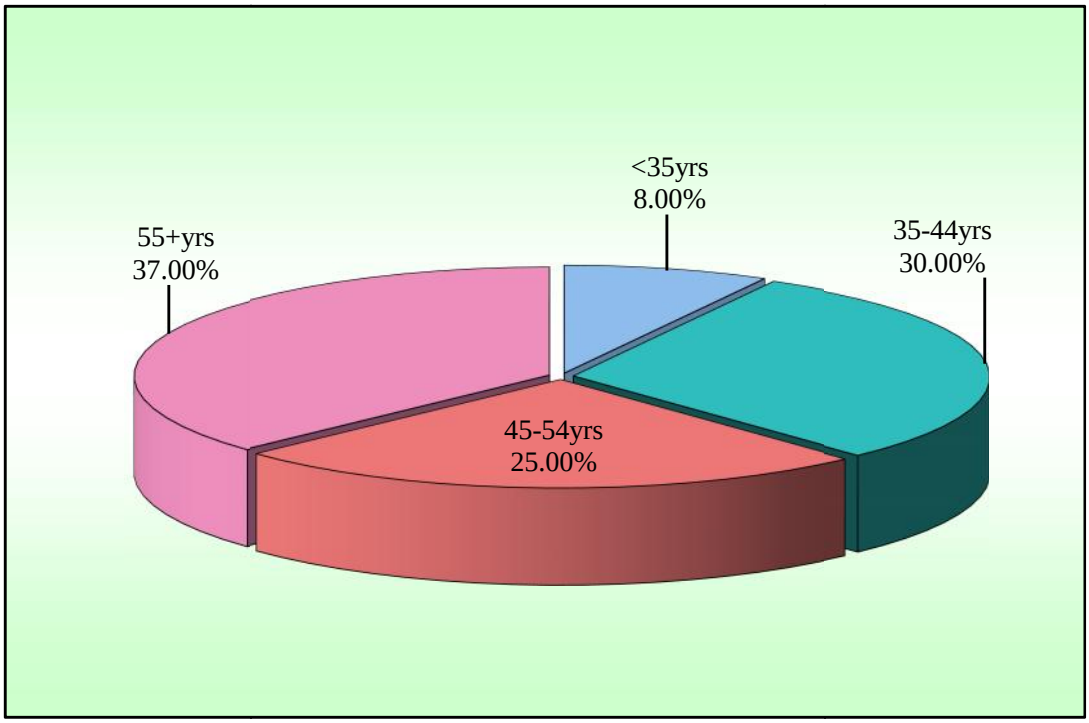
RESULTS

100 patients with cirrhosis were included in the study and were subjected to psychometric tests (NCT-A and DST).

Table 5: Distribution of patients by age groups.

Age groups	No of patients	% of patients	Mean age (years)	SD age
<35yrs	8	8.00	29.00	4.04
35-44yrs	30	30.00	39.60	2.71
45-54yrs	25	25.00	49.28	2.91
55+yrs	37	37.00	61.41	5.78
Total	100	100.00	49.24	11.58

Graph 1 - Distribution of patients by age groups.

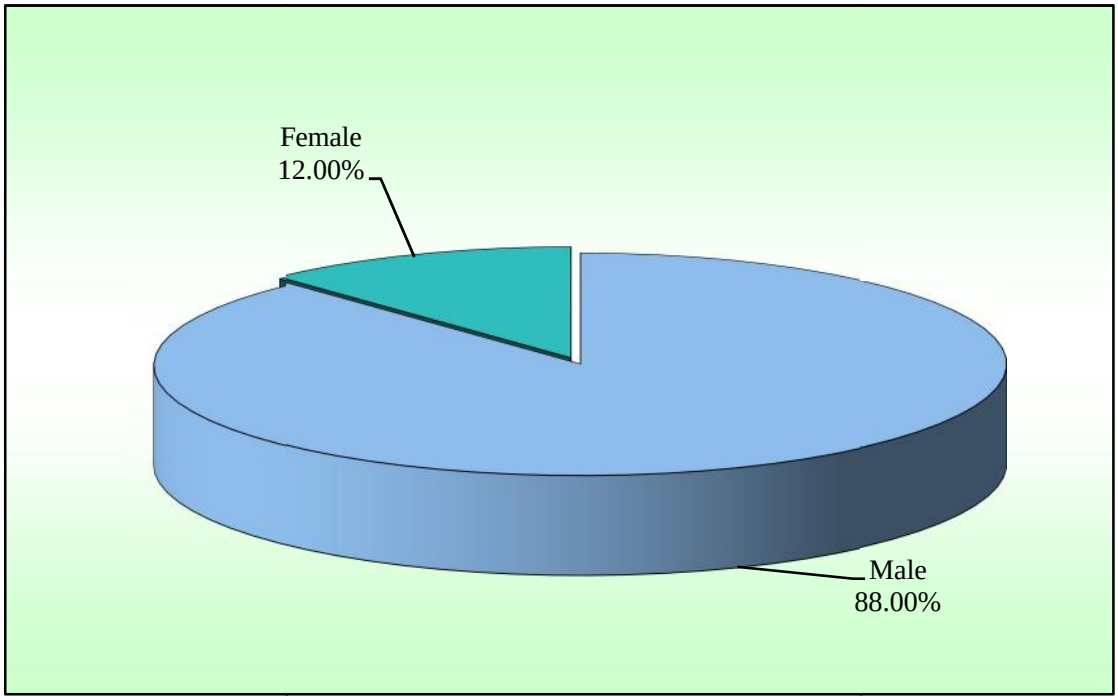


This study consisted of 100 patients with mean age of 49.24 years. 8% (n=8) patients were in the age group of <35 years, 30% (n=30) patients were in the age group of 35-44 years, 25% (n=25) patients were in the age group of 45-54 years and 37% (n=37) patients were in the age group of 55+ years (which was the largest age group in the study).

Table 6: Distribution of patients by sex.

Sex	No of patients	% of patients
Male	88	88.00
Female	12	12.00
Total	100	100.00

Graph 2 - Distribution of patients by sex.

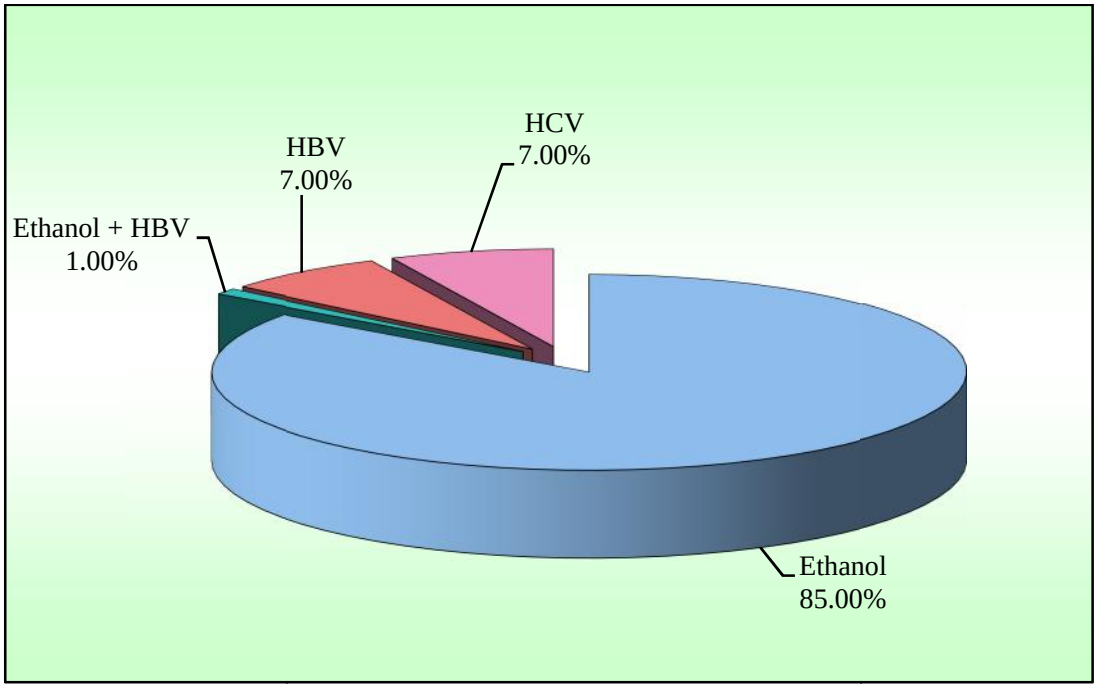


In the present study, 88% (n=88) patients were male and 12% (n=12) patients were female. A male preponderance was observed.

Table 7: Distribution of patients by etiology.

Etiology	No of patients	% of patients
Ethanol	85	85.00
Ethanol + HBV	1	1.00
HBV	7	7.00
HCV	7	7.00
Total	100	100.00

Graph 3 - Distribution of patients by etiology.

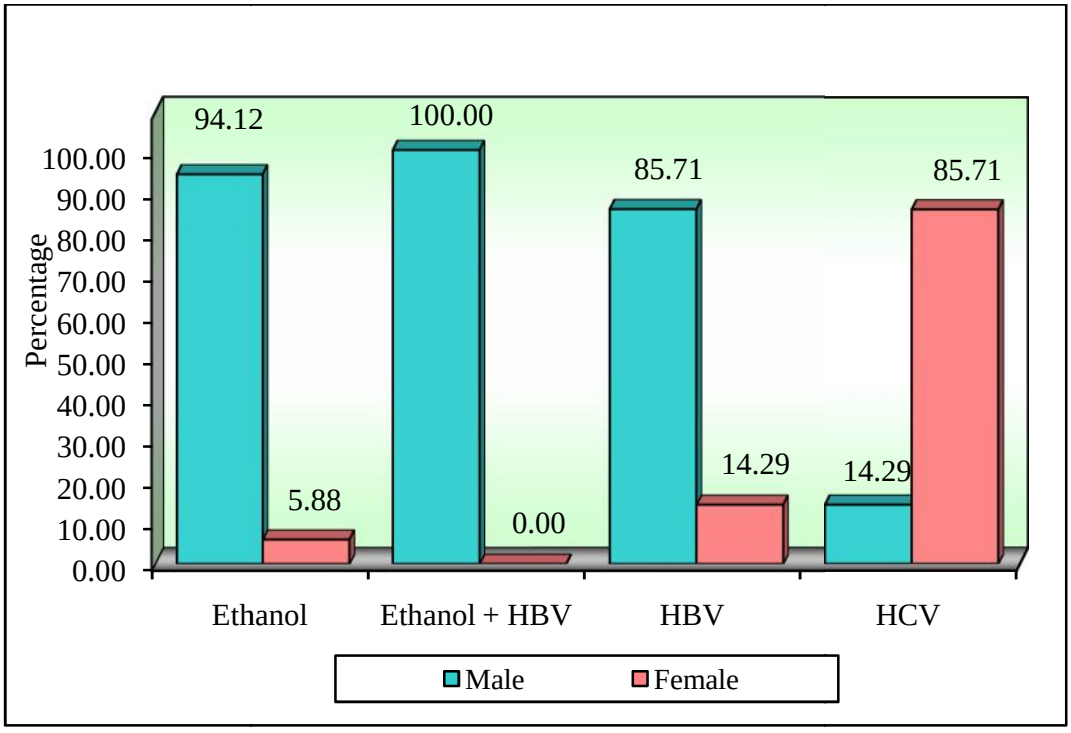


In the present study, the cause of cirrhosis in 85% (n=85) patients was alcohol, in 7% (n=7) was hepatitis B (HBV), in 7% (n=7) was hepatitis C (HCV) while in 1% (n=1) it was combination of hepatitis B with alcohol. Alcohol preponderance was observed.

Table 8: Comparison of male and female patients by etiology.

Etiology	Male	%	Female	%	Total	%
Ethanol	80	94.12	5	5.88	85	85.00
Ethanol + HBV	1	100.00	0	0.00	1	1.00
HBV	6	85.71	1	14.29	7	7.00
HCV	1	14.29	6	85.71	7	7.00
Total	88	88.00	12	12.00	100	100.00

Graph 4: Comparison of male and female patients by etiology.

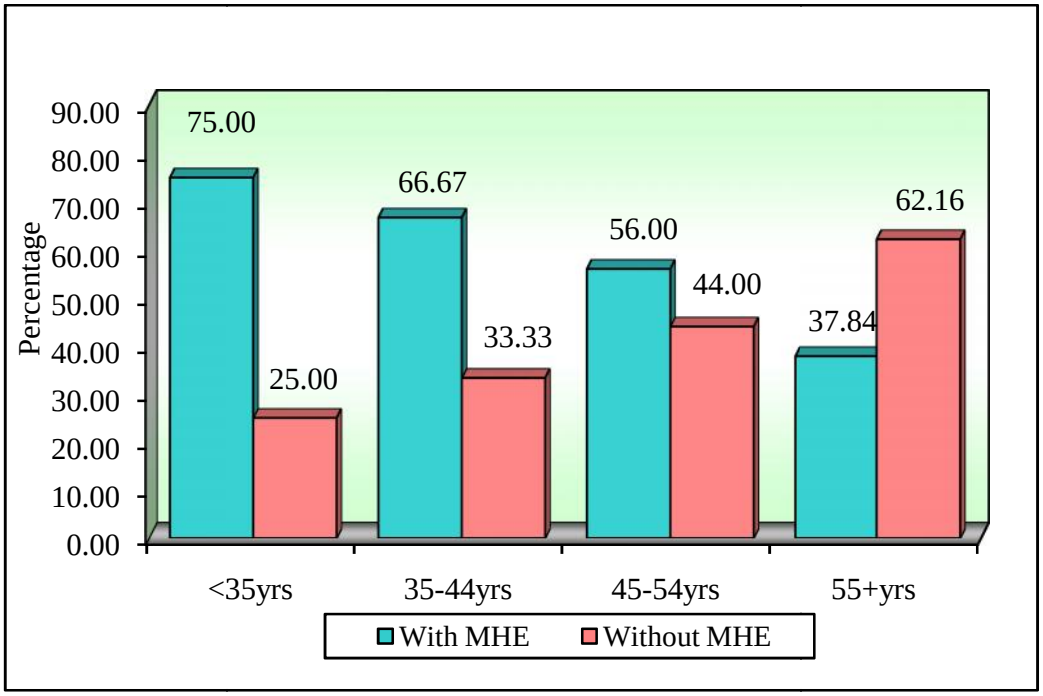


In the present study, 85.71% (n=6) having HCV as etiology of cirrhosis were females while 94.12% (n=80) having ethanol as etiology were males.

Table 9: Association between age groups with status of MHE.

Age groups	Status of MHE				
	With MHE	%	Without MHE	%	Total
<35yrs	6	75.00	2	25.00	8
35-44yrs	20	66.67	10	33.33	30
45-54yrs	14	56.00	11	44.00	25
55+yrs	14	37.84	23	62.16	37
Total	54	54.00	46	46.00	100
Chi-square= 7.2829 P = 0.0631					

Graph 5 - Association between age groups with status of MHE.

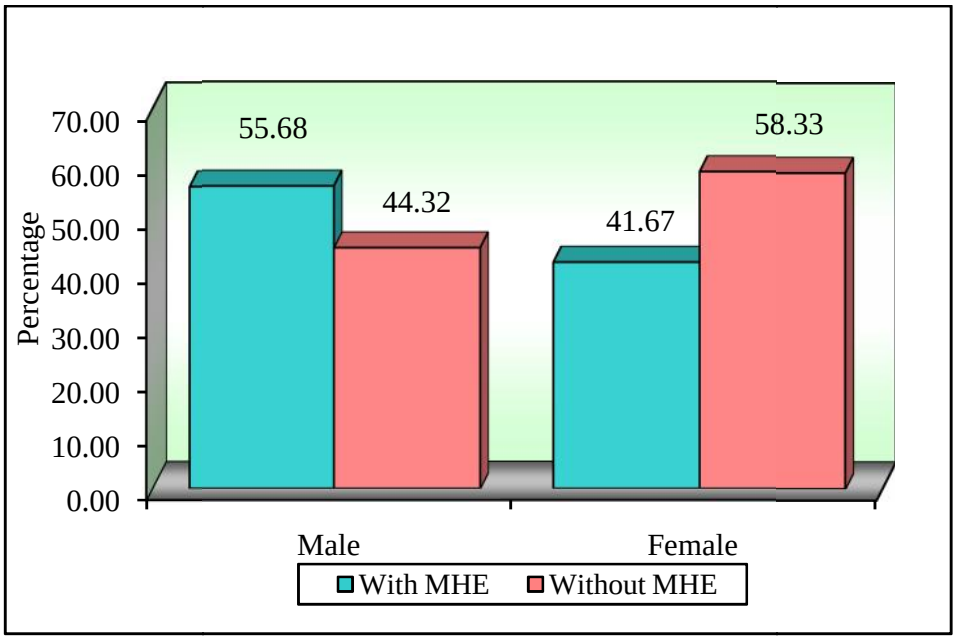


In the present study minimal hepatic encephalopathy was present in 54% (n=54) of the patients according to the diagnostic criteria of the study. Among the various age groups, 75% (n=6) in <35 years age group, 66.67% (n=20) patients in 35-44 years age group, 56% (n=14) patients in 45-54 years age group and 37.84% (n=14) patients in 55+ years age group were found to have MHE. The difference was not found to be statistically significant (p value 0.0631).

Table 10: Association between sex with status of MHE.

Sex	Status of MHE				
	With MHE	%	Without MHE	%	Total
M ale	49	55.68	39	44.32	88
Female	5	41.67	7	58.33	12
Total	54	54.00	46	46.00	100
Chi-square= 0.8352 P = 0.3612					

Graph 6 - Association between sex with status of MHE.



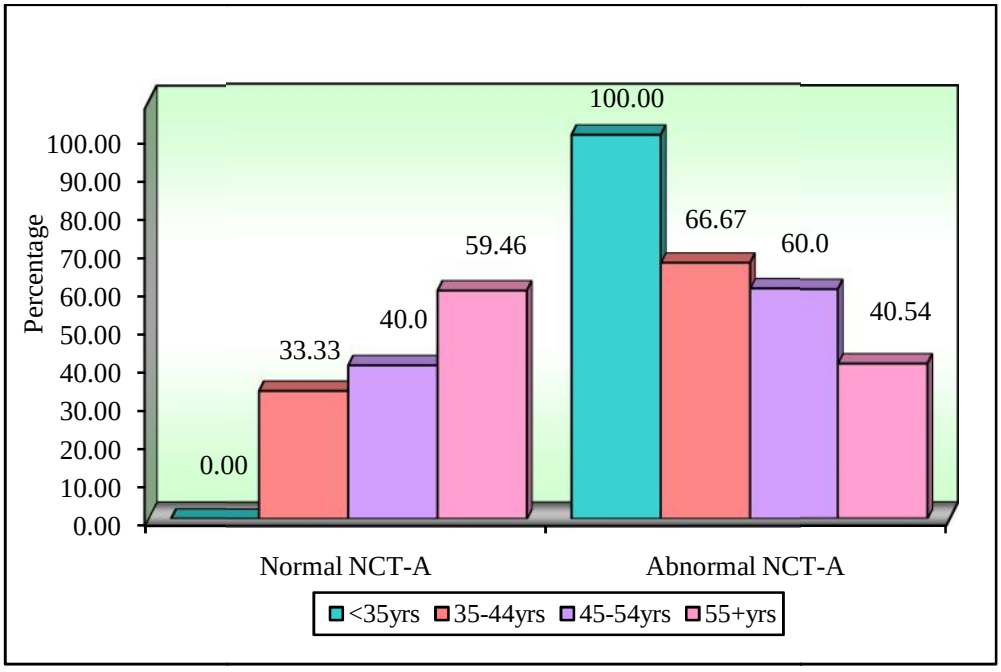
In the present study, 55.68% (n=49) males were found to have MHE and 41.67% (n=5) females were found to have MHE. The difference was not statistically significant (p value = 0.3612).

Table 11: Association between age groups with status of NCT-A.

Age groups	Status of NCT-A				
	Normal NCT-A	%	Abnormal NCT-A	%	Total
<35yrs	0	0.00	8	100.00	8
35-44yrs	10	33.33	20	66.67	30
45-54yrs	10	40.00	15	60.00	25
55+yrs	22	59.46	15	40.54	37
Total	42	42.00	58	58.00	100
Chi-square=11.3892 P = 0.0101*					

*p<0.05

Graph 7 - Association between age groups with status of NCT-A.

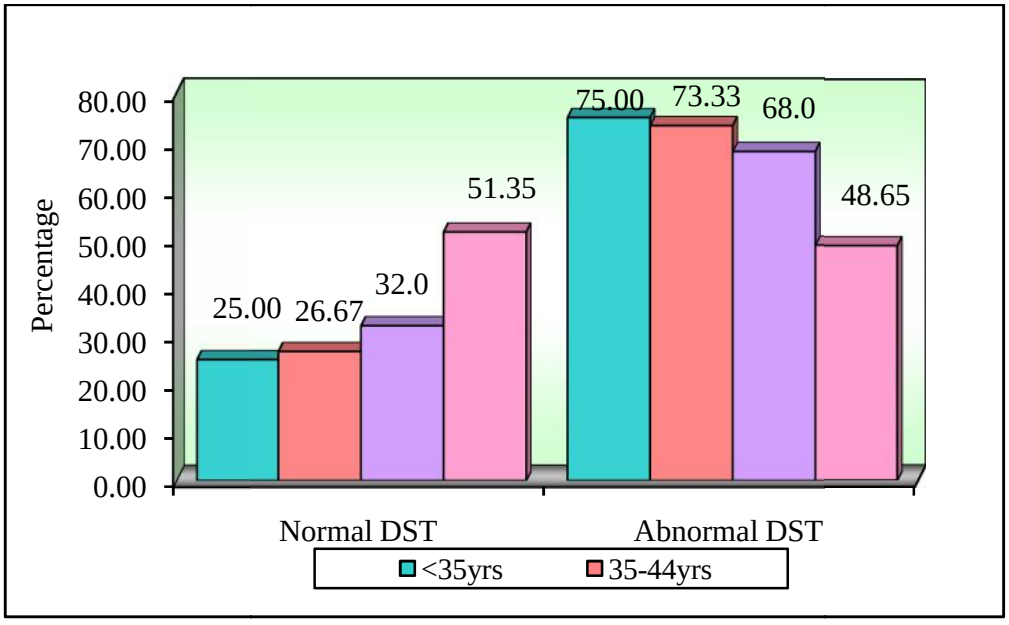


In the present study, NCT-A was found to be abnormal in 58% (n=58) patients. Among the various age groups 100% (n=8) patients in <35 years age group, 66.67% (n=20) patients in 35-44 years age group, 60% (n=15) patients in 45-54 years age group and 40.54% (n=15) patients in 55+ age group were found to have abnormal NCT-A.

Table 12: Association between age groups with status of DST.

Age groups	Status of DST				
	Normal DST	%	Abnormal DST	%	Total
<35yrs	2	25.00	6	75.00	8
35-44yrs	8	26.67	22	73.33	30
45-54yrs	8	32.00	17	68.00	25
55+yrs	19	51.35	18	48.65	37
Total	37	37.00	63	63.00	100
Chi-square=5.4062 P = 0.1443					

Graph 8 - Association between age groups with status of DST.



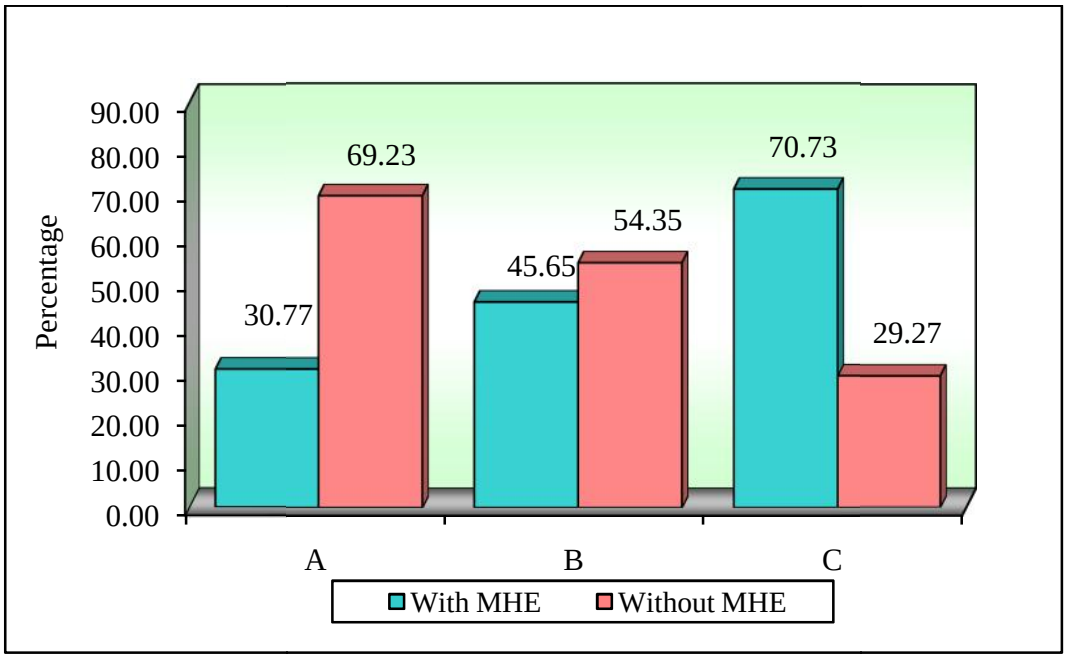
In the present study, 63% (n=63) patients were found to have abnormal DST. Among various age groups 75% (n=6) patients in <35 years age group, 73.33% (n=22) patients in 35-44 years age group, 68% (n=17) patients in 45-54 years age group and 48.65% (n=18) patients in 55+ years age group were found to have abnormal DST. The difference was not statistically significant (p value 0.1443).

Table 13: Association between Child-Pugh class with status of MHE.

Child-Pugh class	Status of MHE				
	With MHE	%	Without MHE	%	Total
A	4	30.77	9	69.23	13
B	21	45.65	25	54.35	46
C	29	70.73	12	29.27	41
Total	54	54.00	46	46.00	100
Chi-square= 9.0622 P = 0.0111*					

*p<0.05

Graph 9 - Association between Child-Pugh class with status of MHE.



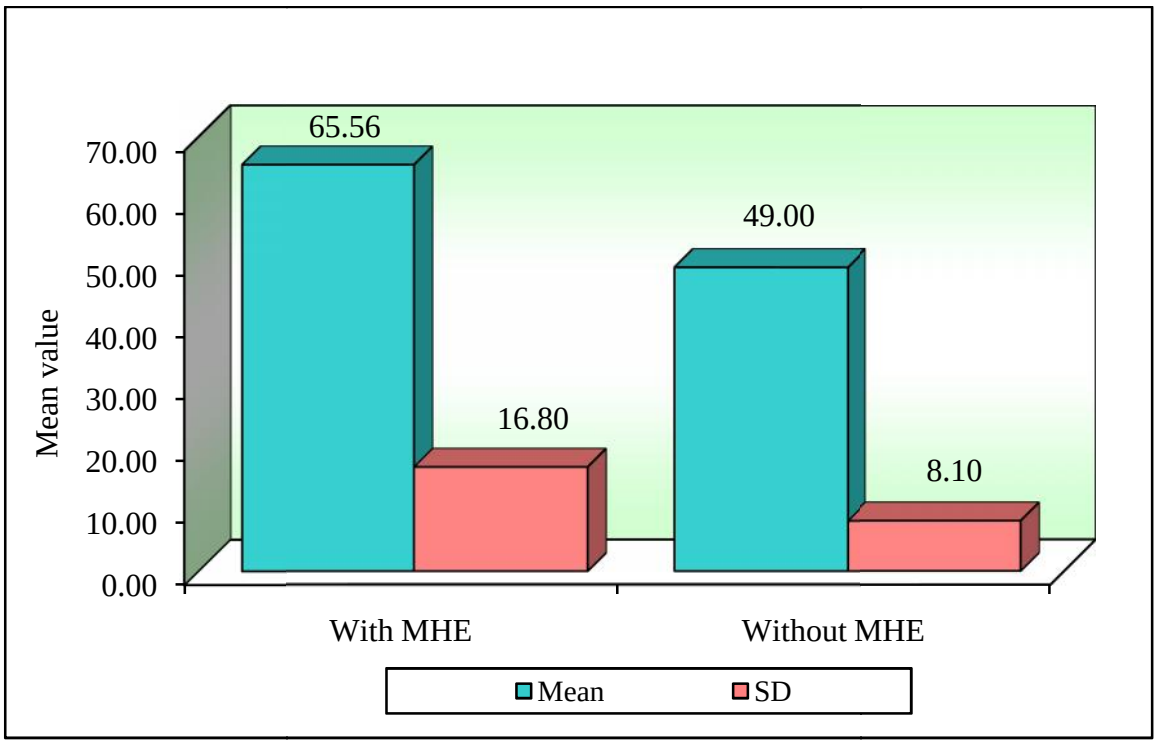
In the present study, 13% (n=13) patients were found to be Child-Pugh class A, 46% (n=46) patients were found to be Child-Pugh class B and 41% (n=41) patients were found to be Child-Pugh class C. Among the various Child-Pugh classes MHE was present in 30.77% (n=4) patients with Child-Pugh class A, 45.65% (n=21) patients with Child-Pugh class B and 70.73% (n=29) patients with Child-Pugh class C. The difference was statistically significant with p value of 0.0111.

Table 14: Comparison of status of MHE with NCT-A score by t test.

Group	Mean(sec)	SD	SE	t-value	p-value
With MHE	68.56	16.80	2.29	7.2093	0.0001*
Without MHE	49.00	8.10	1.19		

*p<0.05

Graph 10 - Comparison of status of MHE with NCT-A score by t test.



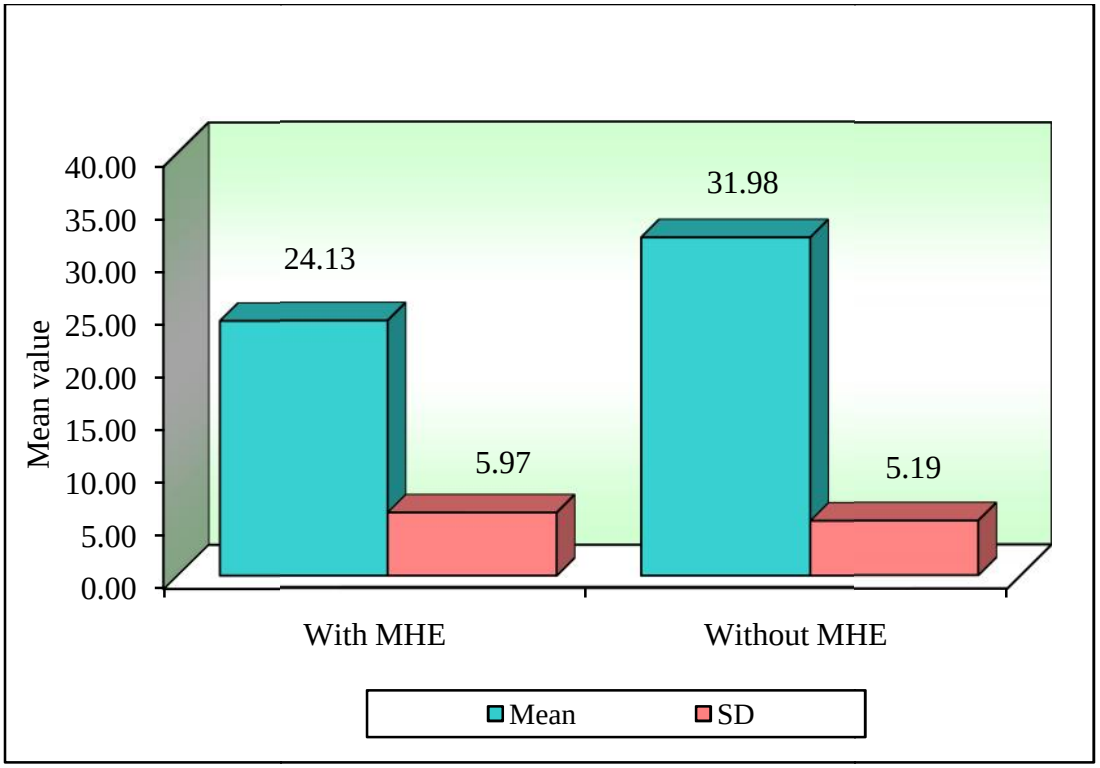
In the present study, a statistically significant difference was observed between the patients with MHE and without MHE (mean values of 68.56 ± 16.80 and 49.00 ± 8.10 respectively) with NCT-A score (t=7.2093, p=0.0001).

Table 15: Comparison of status of MHE with DST score by t test.

Group	Mean	SD	SE	t-value	p-value
With MHE	24.13	5.97	0.81	-6.9539	0.0001*
Without MHE	31.98	5.19	0.77		

*p<0.05

Graph 11 - Comparison of status of MHE with DST score by t test.

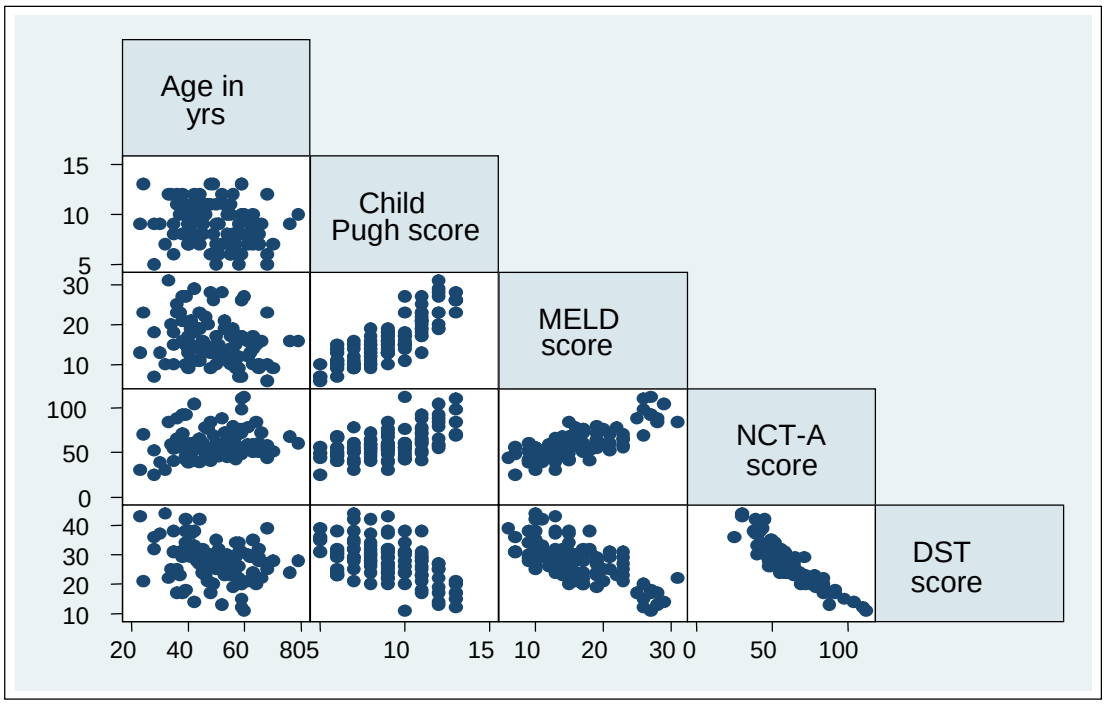


In the present study, a statistically significant difference was observed between the DST score and the patients with MHE and without MHE (mean value of 24.13 ±5.97 and 31.98 ±5.19 respectively) (t= -6.9539, p= 0.0001).

Table 16: Correlation between Child-Pugh, MELD score, NCT-A and DST scores by Karl Pearson's correlation method.

Variables	Variables	r-value	t-value	p-value
Child-Pugh	MELD score	0.8338	14.9526	0.0001*
	NCT-A	0.5371	6.3029	0.0001*
	DST	-0.5175	-5.9869	0.0001*
MELD score	NCT-A	0.7514	11.2746	0.0001*
	DST	-0.6783	-9.1381	0.0001*
NCT-A	DST	-0.9031	-20.8212	0.0001*

Graph 12: Correlation between Child-Pugh, MELD score, NCT-A and DST scores by Karl Pearson's correlation method.



In the present study, Child – Pugh score was seen to correlate well with MELD score, NCT-A and DST score (r value 0.8338, 0.5371 and -0.5175 respectively). MELD score was seen to correlate well with NCT-A and DST score (r value 0.7514 and -0.6783 respectively). NCT-A was seen to correlate well with DST score (r value -0.9031). All the above mentioned correlations were statistically significant (p value 0.0001 for all).

Table 17: Comparison of age groups with other parameters by one way ANOVA.

Variables	Summary	<35yrs	35-44yrs	45-54yrs	55+yrs	Total	F-value	P-value
Hb (g/dL)	Mean	10.31	9.33	10.80	10.62	10.26	1.7962	0.1531
	SD	2.97	2.97	2.54	2.37	2.68		
Platelet count (cell/µL)	Mean	112125	143633	137200	152000	142600	0.3737	0.7722
	SD	64541	100253	82583	117511	100146		
Total bilirubin (mg/dl)	Mean	3.22	6.46	4.15	2.87	4.30	3.3007	0.0236*
	SD	2.72	6.70	3.80	3.64	4.93		
Albumin (gm/dl)	Mean	2.46	2.35	2.59	2.64	2.53	0.7906	0.5020
	SD	0.99	0.68	0.90	0.77	0.80		
PT/INR	Mean	1.97	1.67	1.62	1.48	1.61	2.0885	0.1068
	SD	1.03	0.45	0.55	0.45	0.54		

In present study, the mean Hb was 10.26g/dL, mean platelet count was 142600/ µL, mean total bilirubin was 4.30mg/dL, mean albumin was 2.53g/dL and mean PT/INR was 1.61 with statistically significant interage-group variability being present in total bilirubin levels (p value 0.0236).

DISCUSSION

Hepatic encephalopathy is a dreaded complication of advanced liver disease. A state of subclinical encephalopathy has been described in which the patients with cirrhosis show a number of quantifiable neuropsychological defects even though they have normal mental and neurological examination. The diagnosis of HE is based upon careful neuropsychiatric evaluation. Number Connection Test (NCT-A and NCT-B), Digit Symbol Test have high specificity for HE. In this study we studied 100 patients with liver cirrhosis who had normal mental and neurological examination according to the inclusion and exclusion criteria as defined in the study protocol.

As the normal value of NCT-A and DST differs with age, different age groups were used in our study. The mean age in our study was 49.24 years with maximum number of patients being in the age group of 55+ age group. In a previous study done by Quero et al[87] the mean age was 49 years with range from 17-77 years. The range of patients in a study by Nader et al[94] was 35-71 years with a mean of 51 years. In the present, study males constituted 88% and females constituted 12% of the patients. In a study done by Daniela et al[95] 66% were males and 34% were females. In our study, the etiology was found to be alcohol in majority of the patients (85%). 7% patients had HBV and HCV as etiology while 1% had both HBV and alcohol as the cause. In a study done by Nadar et al[94] 24 patients had hepatitis C, 14 patients had alcoholic cirrhosis, 2 Patients had hepatitis B. In another study done by Daniela et al[95] 43% had HBV, 50% had HCV and 7% had alcohol as the etiology for liver cirrhosis. NCT-A is a test of attention, visual scanning and sequential abilities. DST is a timed test of attention, psychomotor performance and perceptual organisation. In our study, we found abnormal NCT-A in 58% patients while DST was abnormal in 63% patients. In our study, we found prevalence of MHE as 54% without any statistically significant

difference among various age groups. In a study done by Ji-Yao Wang et al[96] prevalence of MHE was found to be 40%. In another study done by Praveen Sharma and Barjesh Sharma in 2010, minimal hepatic encephalopathy was found to be present in 40 – 56% of liver cirrhosis patients.[97] In another study done by Daniela et al[95] MHE was found to be present in 80% of the patients.

In our study, 13% patients fit into Child-Pugh class A, 46% in Child-Pugh class B and 41% in Child-Pugh class C. Child-Pugh grade A was present in 71% of the patients in a study by Quero et al.[87] In a study done by Daniela et al[95] 53% patients were Child-Pugh class B and 47% patients were Child-Pugh class C.

In our study, more severe the liver disease (as quantified by Child-Pugh class and MELD score), worse was the performance in the psychometric tests employed. Similar results were described by Quero et al[87] in their study with majority of the MHE patients belonging to Child-Pugh class C. In a study by Daniela et al[95] 92.86% of the MHE patients were Child-Pugh class C.

In our study, Child-Pugh score and MELD score correlation (r value 0.8338), Child-Pugh score and NCT-A correlation (r value 0.5371), and Child-Pugh score and DST correlation (r value -0.5175) was observed. All the above mentioned correlations were statistically significant (p value 0.0001).

In our study, MELD score was seen to correlate better with NCT-A and DST scores (r value of 0.7514 and -0.6783 respectively), and hence, the diagnosis of MHE was seen to correlate better with MELD score as compared to Child-Pugh score. MELD score and its correlation with NCT-A and DST was statistically significant (p value 0.0001). This was also seen in a study done by Praveen Sharma and Barjesh Sharma[97] with their study showing the p value for MELD score being 0.005 and Child-Pugh score being 0.02 in MHE patients. In our study, NCT-A score correlated

well with DST score (r value -0.9031 and p value 0.0001). In our study, the mean Hb was 10.26g/dL, mean platelet count was 142600/µL, mean total bilirubin was 4.30mg/dL and mean albumin was 2.53g/dL with statistically significant interage-group variability being present in total bilirubin levels. In order to avoid interobserver variability all patients were clinically and neuropsychologically assessed by the same examiner. One of the most important facts in selecting psychometric tests is that we have used age related reference values for measuring the results. NCT-A and DST were selected out of large variety of psychometric tests available because these two tests are reported to be sensitive, and can be administered easily during routine visit to the hospital. However, the NCT-B is reported to be more sensitive than NCT-A hence exclusion of this test may have lowered our diagnostic sensitivity.

CONCLUSION

The presence of MHE in apparently normal individuals is confirmed by our results. This also shows the need to screen all apparently normal cirrhotic patients with such tests. The presence of neuropsychological abnormalities in patients with cirrhosis without any overt signs of encephalopathy is confirmed by our study. Such patients may require treatment for prevention of development of overt hepatic encephalopathy. Moreover their correlation with MELD score and Child-Pugh class may indirectly indicate about poor prognosis in patients with abnormal score. Patients with MHE can be a risk for other people, e.g. while driving. Hence, there is a need to actively screen such patients and inform them regarding the possible complications arising out of it.

SUMMARY

- This study was a cross sectional analytical study of patients with cirrhosis of liver involving administration of two psychometric tests in the form of NCT-A and DST and comparing the values with age-group matched normal values.
- 100 patients with cirrhosis of liver were included in the study fulfilling the inclusion and exclusion criteria. None of the patients had evidence of neurological and/or psychiatric abnormalities on global clinical examination.
- Mean age of the patients was 49.24 years.
- Male preponderance was observed in the study.
- Most common etiology was alcohol especially in males.
- Maximum number of MHE patients were in 35-44 years age group.
- Maximum number of patients belonged to Child-Pugh class B.
- Maximum prevalence of MHE was found in Child-Pugh class C.
- Although both the Child-Pugh sore and MELD score were found to correlate with abnormal test scores but MELD score was found to correlate more with the abnormal values than Child-Pugh class.
- MHE prevalence was found to be 54% in our study.
- Correlation was also seen between NCT-A score and DST score.

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Ref: MDC/DOME/ 221 **Date: 17/11/2014**

To,

Dr. Yogesh om Sharma,
PG student in Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"STUDY OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS OF LIVER",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr.Hema Dhumale)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr.Ganga Pilli)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

INFORMED CONSENT

Title of research study: STUDY OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS OF LIVER.

Principal investigator:-

_____

Post graduate student,

Department of General Medicine,

J.N. Medical College, Belgaum.

Introduction and purpose:-

Hepatic encephalopathy (HE) describes the spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of unrelated neurological and/or metabolic abnormalities. There is a continuum of changes in brain function from 'normal' to overt HE. Functionally impaired brain function with a deficit in intellectual performance, long-term memory and learning capability detected in asymptomatic patients by psychometric or electrophysiological tests is designed as 'minimal HE' (MHE).

A concern in patients with MHE is whether they are at increased risk for driving accidents. Based upon the results of extensive batteries of neuropsychological tests, 44%–60% of patients with advanced liver disease (but without overt clinical signs of HE) were unfit to drive. The same may apply to blue collar workers handling machines or being required to perform high precision tasks.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You may have to give blood and urine samples for the necessary investigations.

Risks and benefits:

The only risk and possible discomfort you might get is while taking blood samples for the investigations. It may cause swelling, pain, redness bruising or infection (rarely happens) at the site from where the samples are drawn.

Benefit is recognising the well defined precipitating factors of hepatic encephalopathy in cirrhosis of liver to prevent mortality.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution/sponsors/compensation:

In case of any injury related to the study, treatment will be made available at KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belgaum. There is no compensation or payment for such medical treatment by law.

Financial incentives for participants:

You will not be paid/offered any gifts/incentives for participating in the study.

Authorisation to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

Questions/contact details:

In case of the queries during study you may contact following persons:

1) Dr_____

Investigator,

PG in General Medicine,

JNMC, Belgaum.

Phone no: _____

2) Dr _____

PROFESSOR,

Dept of General Medicine,

JNMC, Belgaum.

Phone no: _____

Extn: _____

In case of queries regarding your right as participant you may contact:

Dr._____

Chairman,

J.N.M.C, Ethical committee for human research.

Phone no: _____

Extn: _____

CONSENT STATEMENT

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this consent form, and have had all the questions answered.

Name of the participant: _____ Signature/Thumb print: _____

Name of the witness: _____ Signature/Thumb print: _____

Investigator name: _____ Signature: _____

Date: Place:

PROFORMA

CASE No:

NAME: AGE/SEX:

IP NO: ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

PAST HISTORY:

TREATMENT HISTORY:

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITALS: Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Systemic examination:

R.S.:

CVS:

PA:

CNS:

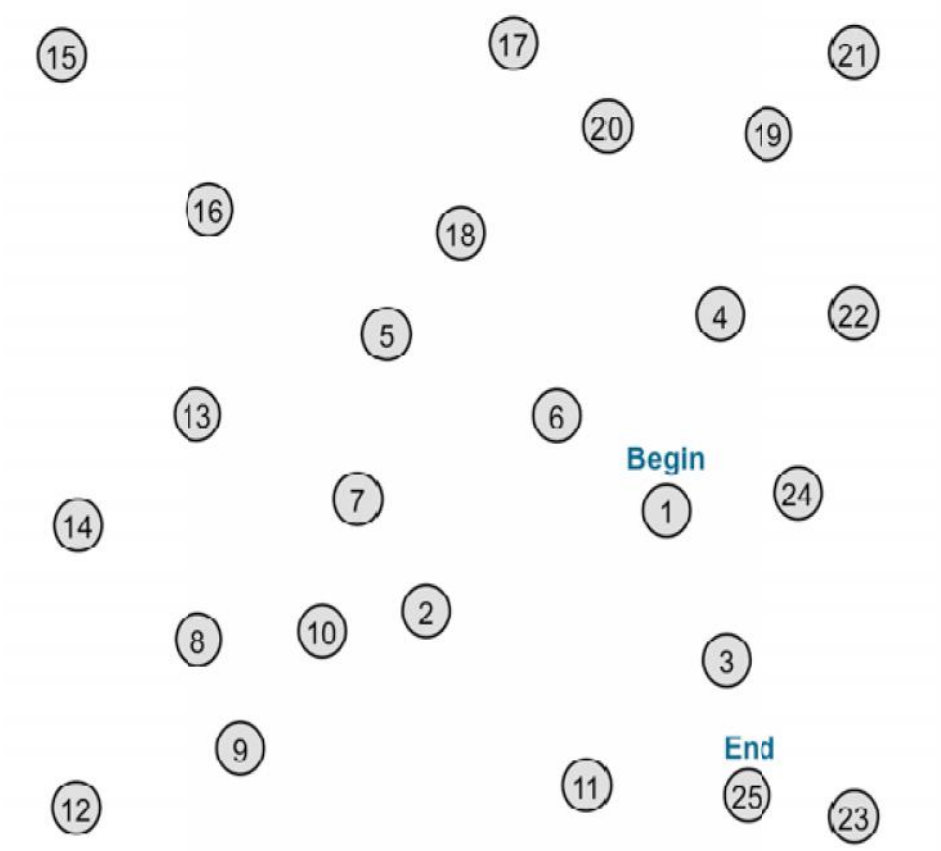
NCT – A TIME: The NCT-A is a test of visuo-spatial orientation and psychomotor speed. The subject is shown a sheet of paper with 25 numbered circles which are randomly spread over the paper. The task is to connect the circles from 1-25 as quick as possible. Test result is the time needed by the subject including error correction time.

DST TIME: The Digit Symbol test (DST) The subject is given a series of double-boxes with a number given in the upper part. The task is to draw a symbol pertinent to this number into the lower part of the boxes. Nine fixed pairs of numbers and symbols are given at the top of the test sheet. Test result is the number of boxes correctly filled within 90 seconds. Pathological test results indicate a deficit in visuo-constructive abilities, especially.

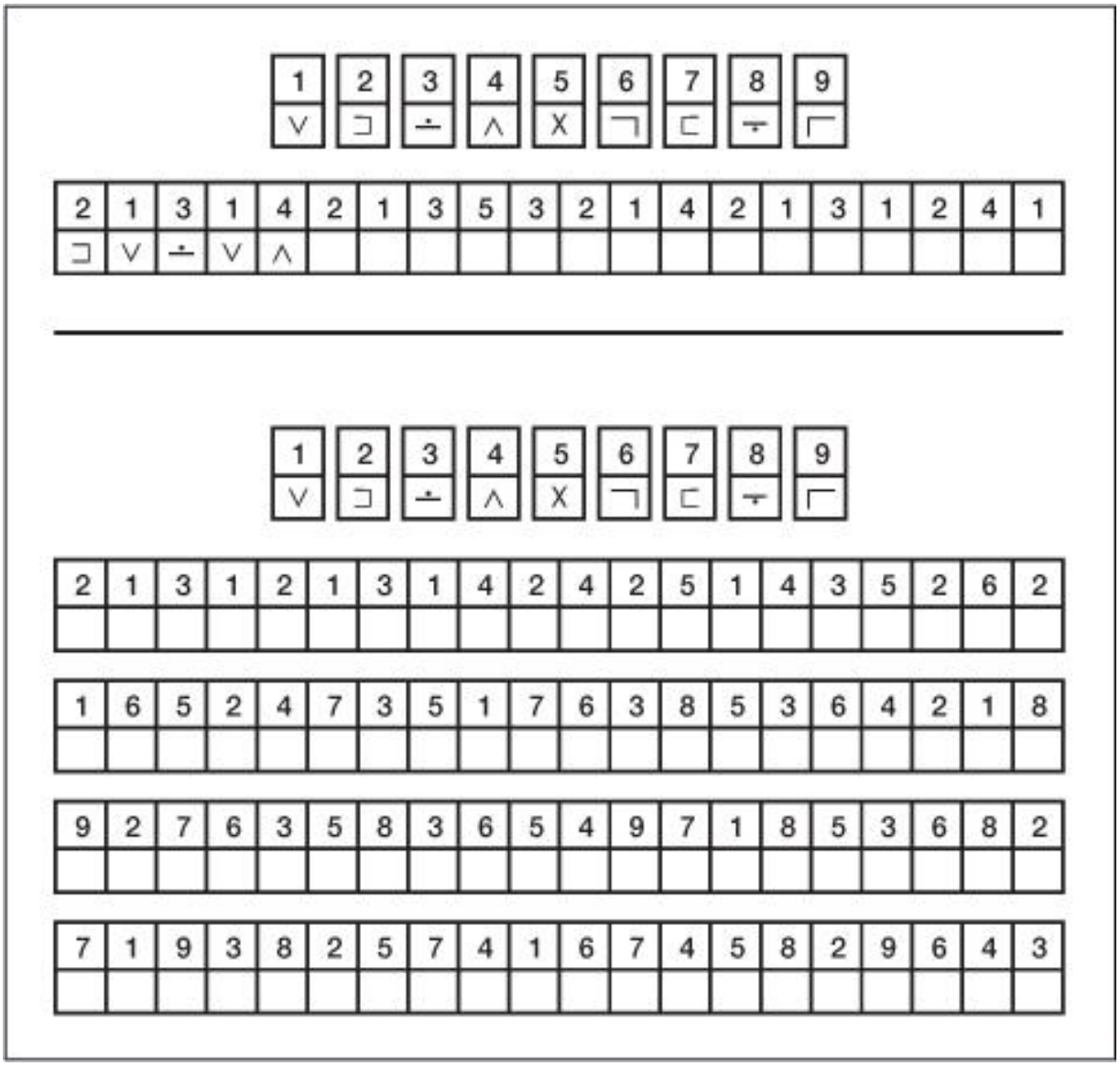
According to the normative parameters for NCT-A and DST established by Bao et al, for Asian population diagnostic criteria for MHE are as follows: time greater than two SD from the mean for the NCT, and score less than two SD from the mean for the DST. For the NCT-A, diagnostic criteria are: > 34.3 s in patients aged < 35 years; > 45.7 s in patients aged 35-44 years; > 52.8 s in patients aged 45-54 years and > 61.9 s in patients aged > 55 years. Diagnostic criteria for the DST are: < 40.5 in patients < 35 years; < 35 in patients aged 35-44 years; < 28.5 in patients aged 45-54 years and < 26 in patients aged > 55 years. Patients with abnormal results from both psychometric tests will diagnosed as having MHE.

INVESTIGATIONS:

1. NUMBER CONNECTION TEST – A



2. DIGIT SYMBOL TEST



ANNEXURE-4- MASTER CHART

KEY TO MASTER CHART

S. No. : Serial No.

IP NO – Inpatient number.

M- Male.

F- Female.

HCV – Hepatitis C.

HBV – Hepatitis B.

Hb – Haemoglobin.

PT/INR – Prothrombin time/International normalized ratio.

MELD score – Model for End stage Liver Disease score.

NCT – A – Number connection test – A.

DST – Digit symbol test.

Sec – time in seconds.