“A STUDY ON MINIMAL HEPATIC ENCEPHALOPATHY IN CIRRHOTICS”

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CERTIFICATE

This is to certify that this dissertation entitled **"A Study on Minimal Hepatic Encephalopathy in Cirrhotics"** submitted by **Dr. R.VINOTH KUMAR to** the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfilment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Hepatic encephalopathy includes a spectrum of transient and reversible neurological and psychiatric manifestations usually found in patients with chronic liver disease and portal hypertension. Its occurrence indicates a poor prognostic factor with a projected one year survival rate of 43%. It occurs in 50% to 70% of cirrhotic patients. The least severe form of hepatic encephalopathy, which is not recognized on clinical examination is Minimal hepatic encephalopathy (MHE). It impairs health related quality of life (HRQOL). It can be detected by using sensitive tests like number connection tests, line tracing tests and figure connection tests, EEG, visual, auditory and somatosensory evoked potentials. Ammonia levels are found to be elevated in patients with minimal hepatic encephalopathy and therefore can play a role in the causation of minimal hepatic encephalopathy. Minimal hepatic encephalopathy has a subtle but negative impact on a patient's spatial and motor skills, the ability to perform complex tasks such as driving, and even quality of life. Some studies have reported that patients with MHE can progress and later on develop overt hepatic encephalopathy. Due to its negative impact on daily living, it has been suggested that the failure to diagnose this condition could be classified as a medical error.

Helicobacter pylori, a gram negative microaerophilic bacteria produces ammonia from urea, which is absorbed in the gastric lumen into circulation.Infection with these bacteria can result in hyperammonemia and hepatic encephalopathy and eradication of these bacteria results in decreased

ammonia levels. However the association of Helicobacter pylori in the causation of minimal hepatic encephalopathy was not studied in detail.

We conducted this study in our department to find out the incidence of minimal hepatic encephalopathy in patients with cirrhosis and to establish a correlation between H.pylori infection in patients with minimal hepatic encephalopathy.

REVIEW OF LITERATURE

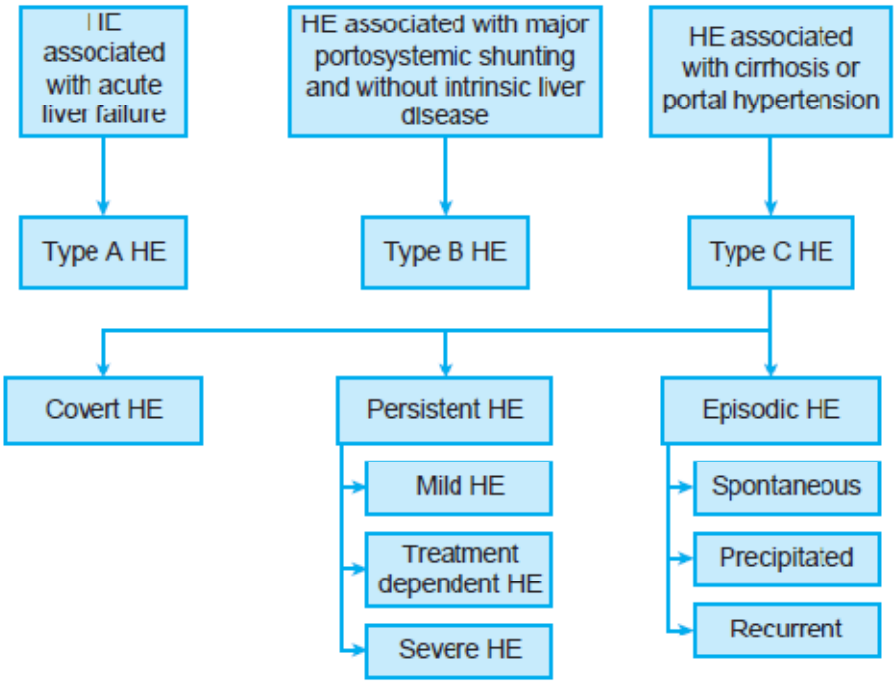
Hepatic encephalopathy (HE) represents a continuum of transient and reversible neurologic and psychiatric abnormalities, varying from subtle altered mental status to deep coma. It is a reversible state of impaired cognitive function or altered consciousness in patients with liver disease. HE is not a single clinical entity. [(1)] It may reflect reversible metabolic encephalopathy, brain atrophy, brain edema, or a combination of these factors. Bajaj and collegues in 2011 presented a data in European association for the study of liver which showed that deficits in psychomotor speed, working memory, response inhibition and attention increase with the severity and number of episodes of overt hepatic encephalopathy.

Hippocrates initially described the neurologic syndromes associated with chronic liver disease whereas Adams and Foley published a series of papers in mid twentieth century on hepatic encephalopathy. [(2)]

Nomenclature

Hepatic Encephalopathy Consensus Group in 1998 at the World Congress of Gastroenterology meeting in Vienna standardized the definitions of the different syndromes in Hepatic encephalopathy. Initially hepatic encephalopathy and portosystemic encephalopathy were interchangeably used.[(3)] But later the term portosystemic encephalopathy was discarded as it is very rare in the absence of intrinsic liver disease. Hepatic encephalopathy wasclassified into three main categories. Type A is associated with acute liver failure, Type B (B for bypass) is associated with portosystemic shunts without

intrinsic liver disease, and Type C is associated with chronic liver failure or cirrhosis. Type A HE, formerly known as alfa HE, is remarkably different from type B and type C.



Episodic HE is characterized by changes in the mental state that vary in severity and duration. These episodes can be either secondary to a known precipitating factor, otherwise called precipitated HE, or can occur in the absence of any recognized precipitating factor, and are called spontaneous HE. Recurrent HE is defined as that which occurs twice or more in 1 year. Persistent HE is defined as the presence of cognitive impairment at baseline (lasting beyond 2 weeks) secondary to liver diseasethat negatively impacts on

social and occupational functioning. The other term that perished during this time of terminology metamorphosis was “subclinical hepatic encephalopathy” [4] Instead, the term “minimal hepatic cencephalopathy” was introduced.

This is defined as HE occurring in patients with liver disease who have completely normal mental status and neurologic examination but who have cognitive deficits in specific neuropsychometrictests . It is seen in a large proportion of cirrhotic subjects and has received a lot of attention by hepatic encephalopathy researchers over the last decade.

Classification and semiquantification of the severity of overt HE was developed by Harold Conn in the 1970s and is well known as the WestHaven criteria.[5] The following table illustrates the modified West Haven criteria along with the operative definition, which was proposed by Amodio et al.[6]

MODIFIED WEST HAVEN CRITERIA

Grade	Description	Operative definition
0	No abnormality detected	
Minimal HE	No neurologic symptoms Normal clinical examination Abnormal psychometric test performance	PHES >2 SD in two or more tests ICT >5 lures CF: critical frequency of 39 Hz or less
1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction	Naming ≤7 animals in 120 seconds Oriented in time and space
2	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behaviours	Disoriented in time (≥3 items incorrect). day of the week day of the month the month the year Oriented in place
3	Somnolence to semistupor Responsive to stimuli Confused Gross disorientation Bizzare behaviour	Disoriented in place (≥2 items incorrect): state/country region/country city place floor/ward Disoriented in time, and reduction in Glasgow coma scale(8–14)
4	Coma, unable to test mental state	Unresponsive to painful stimuli (Glasgow coma scale <8)

CF, critical frequency; ICT, inhibitory control test; PHES, psychometric hepatic encephalopathy score; SD, standard deviation

The term “covert HE” was introduced, which encompasses minimal HE and stage I HE. Covert HE is diagnosed mainly by neuropsychiatric tests as most patients in stage I HE will have very subtle signs of mental status changes.

Minimal hepatic encephalopathy

Minimal Hepatic encephalopathy may be defined as the presence of measurable cognitive defects in patients with liver disease and/ or portal systemic shunting, that are not identified by detailed clinical history and complete neurological examination, including interview of close family members, but are detected by abnormalities in neuropsychometric or neuro physiological tests that can be performed at the bedside and in the outpatient setting, in the absence of other known causes of abnormal cognitive tests.[7]

The true incidence of Minimal hepatic encephalopathy in cirrhotics is unknown. It ranges from 22 – 74% according to various studies.[8] The different incidence rates for MHE reported in various studies may be due to usage of different diagnostic criteria. Defining the cut offs for these neuropsychological tests on the basis of age and education can reduce these variations. Patients with advanced liver disease have high prevalance of MHE.Etiology of cirrhosis doesn't affect the prevalence rates of Minimal hepatic encephalopathy.

Health related quality of life (HRQOL)

Effect on MHE on daily functioning:

Patients with minimal hepatic encephalopathy have cognition impairment which may have a deleterious effect in quality of life.[9] Complex activities like driving, planning are affected whereas basic activities are

preserved. Multiple studies have shown that the daily functioning of MHE patients was affected in a significant manner. Treatment with lactulose improved both cognitive functions and HRQOL[10]

Effect of MHE on driving

Schomerus et al and also Watanabe et al demonstrated thatpatients with minimal hepatic encephalopathy had impaired driving abilities because of deficits in psychomotor function.[11,12] Weinet al also found that patients with MHE had a decrease in cognition which leads to impaired driving skills. Patients withminimal hepatic encephalopathy had higher rates of traffic rule violations as reported by Bajaj et al. A number of studies have shown that navigation is needed for safe driving and patients with MHE have impairment of this skill which can lead to accidents. Therefore, these studies show MHE adversely affects driving skills.

PATHOGENESIS

The exact mechanism of hepatic encephalopathy remains unclear. The gut derived toxins are said to play an important role in the pathogenesis of hepatic encephalopathy and this concept has emerged from the observation that repeated gut lavage leads on to the resolution of hepatic encephalopathy. Overt Hepatic encephalopathy has been observed when ammonia containing resins are introduced into the gut.[13]

Many factors have been implicated in the pathogenesis of hepatic encephalopathy.Among the multiple neurotoxins implicated in the pathogenesis of hepatic encephalopathy, ammonia is the most well- described neurotoxin that is involved.

Ammonia

Ammonia is mainly produced in the colon. Colonic bacteria metabolise proteins and also other nitrogen based products into ammonia.Ammonia was synthesized from glutamine by enterocytes.[14] Ammonia enters the portal circulation, and is usually metabolized and cleared by hepatocytes. The reduced hepatocyte function in cirrhosis contributes to the increased circulating levels of ammonia. Increased arterial ammonia levels were seen in about 90% of patients with hepatic encephalopathy. However, these serum levels are neither specific nor sensitive for hepatic encephalopathy.

In the brain, only astrocytes can metabolize ammonia. The enzyme, glutamine synthase (responsible for metabolizing ammonia) is present only in astrocytes.Astrocytes provide physical and nutritional support for neuronal cells and also helps in keeping blood brain barrier intact and thereby regulates cerebral blood flow. Lockwood et al demonstrated the uptake of ammonia by the neurons in patients with liver disease and hyperammonemia using PET scan with N ammonia.[15] Ammonia also has a role in modulating glutamate neurotransmission. Neurosteroids were induced by ammonia and it leads to

stimulation of GABA-A receptor. Lockwood et al also showed that in patients with MHE, increased permeability surface area product causes the ammonia to diffuse more freely than normal. Because of this encephalopathy due to ammonia can occur inspite of normal ammonia levels.In these patients, increased water in the brain was found by MRI which was demonstrated by Cordoba et al. In these patients, neuropsychological function was well correlated with this finding and it seems to reverses with liver transplantation.[16]

INFLAMMATION

Inflammation contributes to the pathogenesisand also plays a role in the development of overt encephalopathy in patients with MHE .[17] Shawcross et al found that the severity of minimal hepatic encephalopathy doesn't correlate with either the severity of liver disease or the blood ammonia levels.[18] This study also showed that MHE patients had high levels of inflammatory markers than patients without MHE. Various cytokines and the standard markers of inflammationhave been used in examining the role played by inflammationin covert HE.

This is best illustrated by the induction of hyperammonemia using an oral glutamine challenge. Glutamine is rapidly broken down by intestinal glutaminaseand leads to a rapid 2–3 fold elevation of blood ammonia levels. By using a glutamine oral challenge test along with sensitive psychometric

tests, an important phenomenon has been noted. This challenge usually does not alter psychometric performance in most patients unless the systemic inflammatory markers are also raised. Whether this phenomenon is mediated by the blood–brain barrier effects of inflammation or some other mechanism remains to be determined.

The binding of the inflammatory cells or cytokines to cerebral endothelial cells allows them to bypass the normal exclusionary effect of the blood–brain barrier.[19] Whatever be the mechanism, it is imperative to definitely identify and treat any infection that may occur as promptly as possible in patients with hepatic encephalopathy.

INTESTINAL FLORA

Gut flora and endotoxins establish another link between ammonia, inflammation and MHE. Varying degrees of intestinal floral imbalance among cirrhotic patients was demonstrated by Zhao et al. According to his study, increased aerobes and anaerobes are seen but bifidobacterium counts are decreased. Overgrowth of E.coli and staphylococcus species in feces was found in MHE patients as reported by Liu et al .[20] Synbiotics can be used to treat which causes increased fecal non urease producing lactobacillus species. This change can result in decreased ammonia levels and thereby reversal of minimal hepatic encephalopathy.

Natural History

Patients with liver disease are known to have a higher frequency of MHE.[21] MHE can lead to overt encephalopathy, decreased survival and poor quality of life. Hence it is mandatory to know whether treatment can induce an improvement in these outcomes.

Many studies such as Hartman et al, Amodio et al and Saxena et found that patients with MHE developed overt hepatic encephalopathy much more commonly than those patients who did not have minimal hepatic encephalopathy.[22] These studies also showed that patients with minimal hepatic encephalopathy have an increased risk of mortality when compared with patients without minimal hepatic encephalopathy.

Das et al showed that CTP score of more than 6 (Child class B) in these patientshave a higher rate of progression to overt hepatic encephalopathy than patients with minimal hepatic encephalopathy and CTP score less than 6.[23] Minimal hepatic encephalopathy patients who have large portosystemic shunts and usually have a good prognosis. This shows that the mortality in these patients may not be related to minimal hepatic encephalopathy per se, but is probably related to the worseningliver function in patients with minimal hepatic encephalopathy.

Precipitating factors

The precipitating factors include gastrointestinal bleeding, electrolyte imbalance, sepsis, hyponatraemia, hypokalaemia, fluid restriction, excessive diuresis, paracentesis, dehydration,diarrhoea/vomiting, excess protein load,constipation,alcohol misuse, CNS - active drugs, TIPS insertion and surgery.

Diagnosis

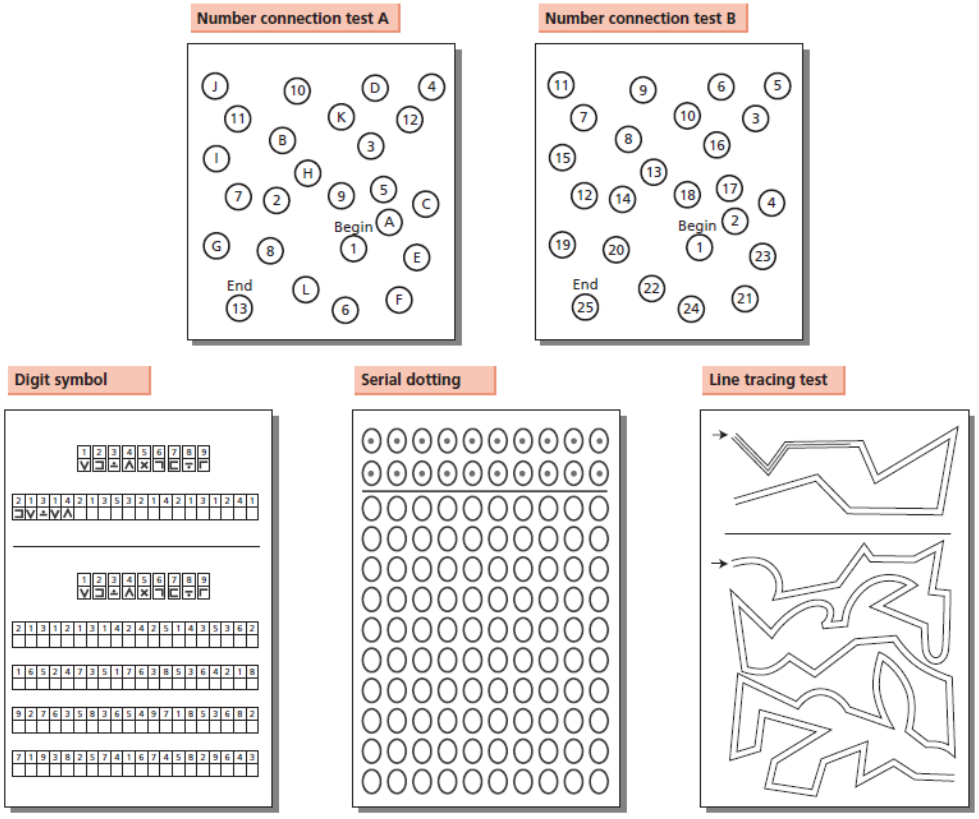
PSYCHOMETRIC TESTS

Psychometric Hepatic Encephalopathy Score

Several batteries of tests for the diagnosis of HE have been studied, and theycenter around detection of deficits in attention and processing speed.[24] These tests help to identify impairment in visuo-spatial function, response time , attention and inhibition, and they are sensitive to the changes that are associated with MHE. The Psychometric Hepatic Encephalopathy Score (PHES) was specifically designed to detect these changes associated with MHE.

It comprises 5 different tests: the number connection test A (NCT-A), the numberconnection test B (NCT-B), the digit symbol test (DST), the line-tracing test (LTT), and the serial dotting test (SDT).This score was devised by Weissenborn, Schomerus et al. based on the Hamster study.[23] Each of the

different tests looks to identify deficits in different areas: NCT-A and NCT-B both evaluate concentration, visuomotor speed and mental tracking, but NCT-B does this with greater complexity.



The DST evaluates the psychomotor and visuomotor speed, while the LTT examines visuomotor and visuospatial skills with special attention given to speed as well as accuracy. Finally,the SDT is a test of psychomotor speed.Ifhowever the PHES is unable to be completed, the Working Group on Hepatic Encephalopathyhas recommended that a combination of any 2 of the

following 4 tests: NCT-A, NCT-B, DST, or block design test (BDT) is necessary to diagnose MHE.

The recommendation is that any impairment in at least 2 of these 5 testsby 2 standard deviations beyond age-matched controls (with equal education) indicatesdysfunction.[25] The disadvantages of the PHES arethat it consumes a lot of time , is often difficult to interpret, a poor test in memory and it is not widely available in the United States of America.

Instead of performing the PHES, Riggio and colleaguesperformed a logistical regression analysis. They first incorporated the scores of all the 5 tests included in the PHES, and then eliminated stepwise the variables that could be removed without impairing regression.This was called the Simplified Psychometric Hepatic Encephalopathy Score (SPHES).[26] Logistic analysis in this study showed that a model that contained only the DST, tSDT, and LTT was similar to that containing all the5 tests.This factor helps in simplifying a test that is already highly regarded in the diagnosis of MHE.

However, SPHES includes the LTT, which requires the longest time to score, and there is also a controversy as to how to interpret its two outcomes: time taken and errors made. The use of the SPHES decreased the total time required for MHE screening but since the NCT-A and B only requirea maximum of 3 minutes, the practical utility of this reduction has not yet been ascertained.

RBANS (Repeatable Battery for Assessment of Neuropsychological Status)

This is an established battery of tests for the assessment of dementia as well as other neurocognitive disorders.[27] This is a paper and pencil test that has four alternate forms (A, B, C, and D) and takes about 20–30 minutes to administer per patient.

This test has extensive normative databases in the 20–89 years age group in the United States of America. Preliminary studies done on patients awaiting liver transplantation showed a close correlation between the MELD score and performance in RBANS.[28]However the main drawback of this test is the remarkable learning effect shown by patients when they are tested at short intervals. This feature limits its utility in assessing the response to treatment.

Computerized psychometric tests

For the diagnosis of MHE, a variety of computer test batteries have been validated over the past few years.[29] Age matched results have been generated. These tests are also available online and can be used either for a nominal fee or free of charge. This test can be administered in an outpatient setting. The inhibitory control test (ICT) and the cognitive drug research (CDR) tests are the most popular testing systems.

Inhibitory control tests

The inhibitory control test (ICT) is a computerized test used to identify traumatic injury to the brain and other psychiatric conditions like schizophrenia, attention-deficit disorder etc. It tests the person for attention and response inhibition ICT measures in response to lures and targets. The reaction times provide an objective measurement of separate but complementary aspects of neurological impairment in MHE.

The lure response is an act of commission and signifies a defect in response inhibition.Response inhibition is an essential aspect of executive function, which allows a subject to inhibit an incorrect response.Impairment of response inhibition is responsible for wrong decisions in psychometric testing and also in everyday life. Quantification of these errors in MHE is possible in ICT.[30] Bajaj et al. validated this system for minimal HE diagnosis by comparing it along with the standard psychometric test (i.e., a paper and pencil test).[31] Here, the subject is shown several letters on a computer screen at 500 ms intervals. The subject is then required to focus mainly on the Xs and the Ys that are interspersed between the other letters.

They are given instructions to respond (by pressing the space bar) wheneveran X is followed by a Y or a Y is followed by an X, (called “target”) and also to refrain from responding when X is followed by X or Y is followed by Y (called “lure”). The subject has to go through six runs of the above test

each lasting 2 minutes in addition to the training run at the beginning. The subjects are graded based on their lure response. More than five lures helps diagnose minimal HE with 88% sensitivity.

Cognitive drug research test

Investigators in Newcastle, UK have validated this testing system in the diagnosis of MHE. CDRT is composed of 7 different tests. It is presented on a computer screen and patients respond with a “Yes/no” response. These scores are reported on a scale of performance in 5 different domains, which include continuity of attention, quality of episodic memory power of attention, speed of memory and the quality of working memory. But, the major limitation of this test is that patients definitely need to undergo a practice session about 1–7 days prior to the test.

Critical flicker fusion frequency test:

In 2002, Kircheis et al. developed this test for the diagnosis of MHE. This neurophysiologic test is based on the principle of hepatic retinopathy.[32]The Muller cells in the retina (similar to astrocytes in brain) are thought to undergo similar changes. This alteration changes the perception of light frequency by the retina of the affected person. Here, light pulses are shown to the patient, initially at higher frequencies of about 60 Hz, and then progressively reducing them by 0.1 Hz/s. At the higher frequencies, the subject perceives the light pulses as a single stream of light. Critical frequency is that

frequency at which the patient first perceives it as discrete light pulses. A critical frequency of <39Hz helps diagnose minimal HE with high sensitivity and specificity, and this test positively correlates with the paper and pencil psychometric tests. This test can be administered in both inpatient and outpatient settings and may take about 15 minutes totally.

An important prerequisite for optimal performance in this test is binocular vision. This test is not influenced by either the education or by occupation of the subject and is widely used in therapeutic trials in the management of hepatic encephalopathy as it can demonstrate improvement without any learning effect. However, limited availability of the test is the main reason for it not becoming popular.

Electroencephalogram

The major finding on EEG is a decrease in the wave frequency along with a general increase in wave amplitude. Initially, theta-waves (frequency 4 to 7 cps) occur which gradually predominate and are then committed by delta waves with a frequency of 1-3 cps. Before termination, there is a loss of wave amplitude along with a flattening of the curve. These abnormalities may be also be found even in cirrhotic patients without any clinical signs of encephalopathy. No relationship was identified between the grade of hepatic encephalopathy and the degree of EEG abnormalities. The sensitivity of using the EEG for the diagnosis of subclinical HE is very limited compared to the

psychometric tests. The EEG is only useful for follow-up examinations, predominantly.[33] Evoked potentials are subdivided into 2 groups (exogenous and endogenous). The exogenous evoked potentials like the flash or checkerboard visual evoked potentials (VEP), brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials are used to examine the function of sensory pathways.

The endogenous evoked potentials are only measures of cognitive function. In the only study that has compared the different exogenous evoked potentials for their sensitivity in diagnosing hepatic encephalopathy, the BAEP was found to be the most sensitive measure for the diagnosis of HE. The most sensitive test in evoked responses is p300 peak obtained in an auditory oddball paradigm. These tests can be used to supplement neurological or neuropsychiatric examination. Overt encephalopathy develops in cirrhotics with abnormal p300 event related potentials than in patients who don't have any such abnormality.

Treatment of MHE

Ammonia plays a main role in the pathogenesis of MHE. Empirical therapy is based on the principle of decreasing the production and absorption of ammonia in the gut for which many agents have been found beneficial.

Nutritional interventions

The European Society for Parenteral and Enteral Nutrition has recommended in 2006, that patients with cirrhosis should eat at least 1.2 g/kg of protein daily. It also recommended that the diet in these patients should be supplemented with branched-chain amino acids (BCAAs) and vegetable protein whenever hepatic encephalopathy has developed. Vegetable-based protein has been found to be better tolerated by patients with cirrhosis than the meat-based protein.

Pharmacological therapy

Non-absorbable disaccharides include lactulose and lactitol. Lactulose reduces blood ammonia levels by various mechanisms thereby helps in treating MHE. Lactulose should be started at a dose of 30 to 60ml per day. Appropriate duration of therapy was not known although some studies recommend to uselaculose for 3 to 6 months. Treatment of MHE with lactulose improves the patient's quality of life and psychometric performance.[34] Kale *et al*. reported that the interstitial brain edema resolves after treatment for 3 weeks with lactulose in patients with MHE and also noticed improvement in the neuropsychiatric performance.[35]

Prasad *et al*. also reported the effectiveness of lactulose in patients with MHE. He reported that following treatment with lactulose for 3 months, the psychometric tests which was abnormal previously were normalized and

patients quality of life was also improved. These findings were confirmed by another study which compares lactulose, prebiotic and LOLA along with no treatment. Lactulose or lactitolare considered as intestinal probiotics with various actions on the gut flora. A meta-analysis ofvarious randomized trials showed lactulose improves quality of life in patients with minimal hepatic encephalopathy. Branched-chain amino acids, flumazenil, L–ornithine L–aspartate, acetyl L-carnitine, and probiotics/synbiotics are also tried in the treatment of MHE with varying results.

Prebiotics, probiotics or synbiotics

These drugs are useful in treating minimal hepatic encephalopathy and can be used over a long period for treating MHE.[36,37] Liu *et al*. reported that acidifying gut lumen by altering the gut flora using synbiotics results in decrease of E.coli and staphylococcal species which are urease producing organisms and increase in non urease producing organisms thereby causes reduction of ammonia levels and reversal of MHE in 50% of patients. A randomized trial showed that patients with MHE improved after the supplementation of probiotic yogurt which shows probiotics also have a role in the treatment of MHE. Several studies reported that probiotics improves the patients quality of life.[38] All these drugs reduce the bacterial urease activity thereby reducing the production of ammonia. Additionally, it also causes increased clearance of ammonia by hepatocytes by reducing oxidative stress

and inflammation in the hepatocytes. Therefore it is clear that probiotics can be used in the treatment of MHE and can be used as an alternative to lactulose.

L-ornithine–L-aspartate

The effectiveness of LOLA in the treatment of MHE is not proved. A recent study reported that LOLA is as effective as probiotics and lactulose in treating MHE. That study also stated that MHE patients after treatment with LOLA had better quality of life and normalization of psychometric tests. However further studies are needed to confirm the effectiveness of LOLA in treating MHE.

Antibiotics

The effectiveness of antibiotics in treating MHE is controversial. Metronidazole,[40] vancomycin, paramomycin etc., have been reported to reverse HE [41]. Probably, the major mechanism of action of these antibiotics is in the small intestine where bacterial overgrowth has beenreported.Further studies are needed with these antibiotics to assess the efficacy in MHE.

Helicobacter Pylori

Helicobacter pylori is a gram-negative microaerophilic bacterium recognized as the primary etiologic agent for gastric cancer. The H.pylori bacterium has been designated as a definite carcinogen by the International Agency for Research on Cancer (IARC).

Helicobacter pylori are unique bacteria suited to live in the acidic environment that is present in the human stomach. The spiral shape of the bacterium and multiple unipolar flagella protects the organism from low pH.H.pylori produces urease which is responsible for the production of ammonia from urea. They produce large amounts of urease, an enzyme that hydrolyzes urea to alkaline ammonia and carbon dioxide.The multiple routes of transmission are fecal-oral, oral-oral or gastro-oral route.(42)

One more source of bacterial transmission is infected gastric secretions. Transmission can also occur with improper disinfection of endoscopes and accessories.(43)

H. pylori showsstrict affinity for the gastric mucosa and the intestinal epithelium with gastric metaplasia.It does not colonize gastric epithelium with intestinal metaplastic change, as the production of antimicrobial factors select against colonization. Helicobacter pylori very rarely colonize the deeper parts of the gastric glandular mucosa since O-glycans present there impair its growth.(44) H.pylori reduces the secretory leukocyte protease inhibitor (antibacterial molecule) which could prevent the infection from persistence.

Most of the ammonia originates from the gut, where it is produced by the bacterial flora. The stomach, when infected with *H. pylori* is an alternative site of ammonia production. In a normal person, the ammonia is extracted by

the liver and therefore, in liver failure, large quantities of ammonia reach the systemic circulation due to porto-systemic shunting and impaired ureagenesis.

The causal role of *H. pylori* as a cause of hyperammonaemiain persons with liver cirrhosis has not been fully clarified. The reduction in the blood ammonia levels seen after *H. pylori* eradication in some studies has been attributed to the nonspecific effect of antibiotic therapy on the ammonia producing gut flora rather than the eradication of H.pylori.

NONGASTRIC DISEASES AND H.PYLORI INFECTION

H.pylori infection is associated with a number of diseases like scleroderma, acne rosacea, thyroidits, guillianbarre syndrome, raynauds etc. Although it is postulated , evidence supporting an association with the above mentioned diseases is weak.[45]

H.Pylori and MHE

H.pylori causes increased ammonia production. The role of H.pylori in causing minimal hepatic encephalopathy has not been well studied. But some studies reported an increased prevalance of H. pylori in patients with MHE and that eradication of H. pylori leads to a decrease in the serum ammonia levels.

Study showing increased incidence of H.pylori in patients with MHE

1. Role of Helicobacter Pylori infection in the pathogenesis of MHE and effect of its eradication – AvinashAgarwal, Alok Gupta, Mam Chandra.[46] Indian J Gastroenterol (Jan-Feb2011) 30(1):29-32.

This study shows that there is a significant association between the presence of H.pylori and MHE in cirrhotic patients and anti H.pylori treatment resulted in the reduction in blood ammonia levels and also correction of MHE.

Diagnostic Tests for *Helicobacter pylori*

During an endoscopic procedure, 3 methods can be used to identify H.pylori.They are the urease test of biopsy specimen, histopathological examination and culture. Urease test of biopsy specimen has been proposed as the initial test of choice since the method is quick, relatively inexpensive, generally accurate and easy to perform.

The gastric tissue specimen is tested for urease activity by putting many bits of tissue in a medium containing pH reagent and urea. Urease produced by H.pylori hydrolyzes urea and liberates ammonia, which produces an alkaline pH and this results in a change in colour of the test medium.[47] The test results can be read within a few minutes to hours. This test is less costly than histological examination. Therefore, a cost-cutting measure is to delay sending tissue for histological examination till urease test results are available. Urease tests are 95% to 100% specific with false-positive tests being not very

common. Accuracy of the urease test can be affected by the presence of blood in the stomach and also recent or current use of drugs such as bismuth-containing compounds, antibiotics or PPIs. A negative urease test therefore cannot exclude *H. pylori* infection in an individual taking the above medications. Testing biopsy tissues from various regions of the stomach, stop offending drug for a few weeks and delayed UGI scopy can improve the sensitivity of the test.

Histopathological examination of the gastric mucosa isn't necessary for the diagnosis of H.pylori. However, this test may provide information about the activity of Helicobacter pylori and mucosal inflammation severity. Apart from this, histological examination can also detect the presence of metaplasia, dysplasia, and neoplasia.Biopsy of "clinically suspicious" areas, multiple biopsies, taking samples from both the lesser and greater curvatures of gastric antrum as well as the body should be done mainly when searching for atrophic gastritis and/or intestinal metaplasia. Histopathologic exam is said to be the gold standard for confirming H.pylori infection. This test has a sensitivity of 95% and a specificity of 98%.[(48)]With the use of special stains like giemsa and genta, the detection rate is higher[(49).]

H.pylori is difficult to culture since the organism is very fastidious, grows slowly and requires specialized media and growth environment.The tissue obtained for culture should be placed in a container with only few drops of saline. Culture is not routinely recommended and indicated only in patients

with refractory disease in whom antibiotic sensitivity is needed to start subsequent treatment.[50]

Nonendoscopic tests are usually used to diagnose *H. pylori* infection, and the most popular method used is serology. IgG antibodies can be detected by ELISA to many bacterial antigens. Testing IgA and IgM class antibodies are not reliable and are not routinely recommended. The advantage of Serology is inexpensive, noninvasive. Serology is ideal for a primary care setting. The sensitivity of serology is high which is around 90 to 100%, its specificity varies from 76% to 96%.

The specificity is highly variable in low prevalence areas. In places where the infection is uncommon, the NPV of serology is high while the corresponding PPV is poor.Hence, before starting treatment the positive serology should be reconfirmed by a second method such as urea breath test or stool antigen test.Because of this, some studies suggest to use a test which helps to detect active infection initially.

The eradication of infection is suggested by the conversion of previous serological test to a negative one after treatment. But, for many months to years the serology remains positive. Because of this serologic scar , it is not used to confirm eradication of H.pylori. Urea breath test detects active *H. pylori* infection. It is also useful in making primary diagnosis, to confirm eradication and to confirm the serology.[51] The principle of Urea breath test is orally

administered urea that is tagged with a carbon isotope, either 13C or 14C is hydrolysed by bacteria and produces ammonia and tagged CO_2, which can then be detected in breath samples.Since non radioactive isotope is used it can safely used for testing pregnant women and children.

The sensitivity of UBT is 88% to 95% and specificity is more than 95%. Patients with antisecretory medications, ppi can have false negative results and the accuracy can be improved by stopping the drugs before testing. It is also not appropriate in patients with previous gastric resection.

Another nonendoscopic method used is an immunoassay to detect the presence of stool bacterial antigens. This test is used to diagnose active *H. pylori* infection. It is also useful in confirming eradication of H.pylori. The sensitivity is 94% and specificity si 97% which is comparable with urea breath test.

Traditional lab based stool test is accurate than rapid stool antigen test. Drugs can affect the sensitivity of the stool antigen test like UBT. Hence interfering drugs should be stopped appropriately before testing.

TREATMENT

Various regimens are available for treating H.pylori. Sequential regimen consists of 10 day therapy with a ppi, amoxicillin both given twice a day for the first 5 days followed by clarithromycin 500mg and tinidazole 500mg for the next 5 days. The eradication rates with sequential regimen is 89% which is higher than the conventional triple therapy.

It was effective in patients infected with clarithromycin-resistant organisms (89% vs. 29%).[52] Multiple studies have confirmed the efficacy of this sequential therapy.Eradication rates are much lower with dual regimens and hence they are no longer recommended for treating H.pylori.[53]

One of the first regimen used to treat H.pylori is Bismuth-based regimen. This regimen consists of bismuth subsalicylate, metronidazole, tetracycline and a ppi given four times a day for 14 days gives almost 80% eradication rate. Because of the large number of tablets, frequent dosing and side effects this regiment was not well tolerated and hence it is considered as a second line regimen.[54]

In united states, bismuth, metronidazole and tetracycline are available in a single capsule to simplify the bismuth based treatment. In a comparative study, patients treated with three of the above capsules four times a day and a PPI twice a day in combination for 10 days had comparable eradication of

H.pylori with thosepatients treated with traditional PPI triple therapy (88% vs. 83%).[55]

Eradication rates of various regimens varies. The eradication rate is 46% for ppi dual regimen, 76% for bismuth based regimen, 80% for ranitidine and bismuth based regimen and 70% for ppi triple drug regimens.[57] Eradication rates are higher when two antibiotics are used instead of one.

If H.pylori is not eradicated in the previous one or two regimens then, rescue therapy is recommended. In rescue therapy, amoxicillin 1gm, levofloxacin 250mg and a ppi is given for 10 days. The eradication rates with rescue therapy is 80%. Rifabutin containing regimen is also used for eradication H.pylori infection. In this regimen rifabutin300mg , amoxicillin 1 gm and a ppi each twice daily is used for 10 days. The eradication rate of this regimen is 85%.

Initially ppi with triple therapy is recommended for eradication of H.pylori infection. If clarithromycin resistence is suspected, then patients should be started on sequential therapy.[58] Bismuth containing regimen or ppi triple regimens can be used for retreatment.

HelicotecUT – rapid urease test

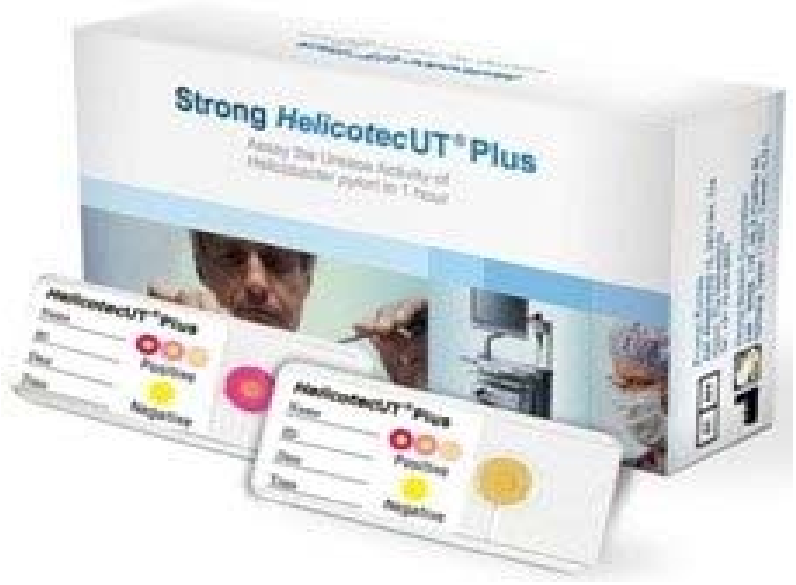
Helicotec UT is designed to detect the urease activity of Helicobacter pylori in gastric mucosal biopsies. H.pylori produce large amounts of urease

which hydrolyzes urea into ammonium ion and bicarbonate. When a tissue specimen is immersed in the Helicotec UT test gel, the elevated pH level due to the presence and activity of urease is indicated by the change in colour of pH indicator in the test gel.

If the gel changes colour from yellow to pink or red, the test is regarded as positive whereas if the gel colour remains yellow after 24 hours, then the test is considered negative.

RAPID UREASE TEST KIT USED IN THIS STUDY-

HelicotecUT® PLUS



AIM AND OBJECTIVES OF THE STUDY

1. To study the incidence of minimal hepatic encephalopathy in asymptomatic cirrhotics.

2. To study the prevalence of helicobacter pylori in asymptomatic cirrhotics with minimal hepatic encephalopathy.

MATERIALS AND METHODS

This is a hospital based prospective study conducted in our Department of Digestive Health and Diseases(DDHD), Government peripheral hospital, Chennai from August 2012 to January 2013 on 50 patients with cirrhosis of liver without overt encephalopathy.

- All patients were subjected to liver function tests, serum creatinine, prothrombin time, Hbsag, Anti Hcv, ultrasound abdomen and gastroscopy.
- Psychometric tests were done to all patients.
- Helicobacter pylori testing was done by rapid urease test (helicotec UT, Strong biotech corp, Taiwan).
- Ethical committee approval was obtained from Kilpauk medical college before starting the study.
- Written informed consent was obtained from all participating subjects in regional language (Tamil). Privacy was ensured.
- Statistical analysis was done by statistical analysis software SPSS (version 17.0).

Psychometric tests

All study patients underwent 5 psychometric tests. NCT-A, NCT-B, Line tracing, Serial dotting and Digit symbol test were performed in all patients. The procedure was briefed to all the patients before the test and the patients were given a trial run before the tests.Exact time taken for each test was recorded and normative values were obtained from 30 control subjects.

Diagnosis of MHE was made when there is significant reduction i.e., > 2 standard deviations from appropriate normative population in 2 or more tests.

INCLUSION CRITERIA

- Patients with cirrhosis without overt hepatic encephalopathy.
- Age 30 -70 years.
- Both sexes
- Patients with cirrhosis of liver in ultrasound and CT

EXCLUSION CRITERIA

- Age below 30 years and above 70 years.
- Patients with overt hepatic encephalopathy (based on clinical examination)
- Patients with history of recent GI bleed.
- Patients with neurological illness,
- Patients with poor vision
- History of H. Pylori eradication treatment in previous 3 months.
- History of any antibiotics intake in the past 2 weeks
- Patients with severe comorbid illness

RESULTS AND STATISTICAL ANALYSIS

A total of 50 patients were recruited for this study.

Table 1 shows the cut off values for 30 normal controls.

Diagnosis of MHE in study group was made when there is significant reduction i.e., > 2 standard deviations from control group in 2 or more tests.

Table 1 : Descriptives for control only

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
NCT_A	30	30	100	58.20	16.961
NCT_B	30	55	165	113.67	29.388
Line tracing	30	55	150	91.57	23.018
Serial dotting	30	50	105	70.67	17.207
Digital symbol	30	15	28	20.67	3.680
Valid N (listwise)	30				

Based on the results , 35 (70%) of the 50 patients had minimal hepatic encephalopathy. In NCT-A, 35 patients in the study group were abnormal. In NCT-B, 34 patients had abnormal results. The abnormal results in line tracing,

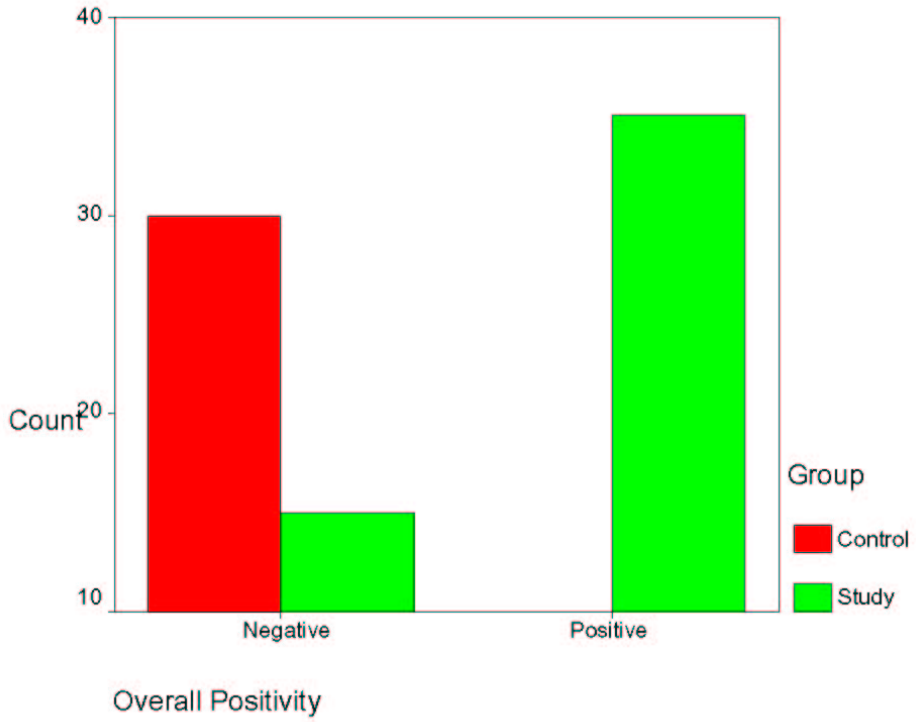
serial dotting, digital symbol test were 34,37,36 respectively. In our study the incidence of MHE in asymptomatic cirrhotics was 70%.

Overall Positivity

Crosstab

			Group		**Total**	**P value**
			Control	**Study**	**45**	
Overall Positivity	**Negative**	**Count**	**30**	**15**		
		% within Overall Positivity	66.7%	33.3%	100.0%	
		% within Group	100.0%	30.0%	56.3%	
	Positive	Count	0	35	35	< .010 (highly significant)
		% within Overall Positivity	.0%	100.0%	100.0%	
		% within Group	.0%	70.0%	43.8%	
Total		Count	30	50	80	
		% within Overall Positivity	37.5%	62.5%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

Highly significant at 1% level


40
30
20
10
Count
Negative
Positive
Overall Positivity
Group
Control
Study

In our study, MHEpatients had no significant relationship with age, Child-Pugh grade and etiology of cirrhosis.

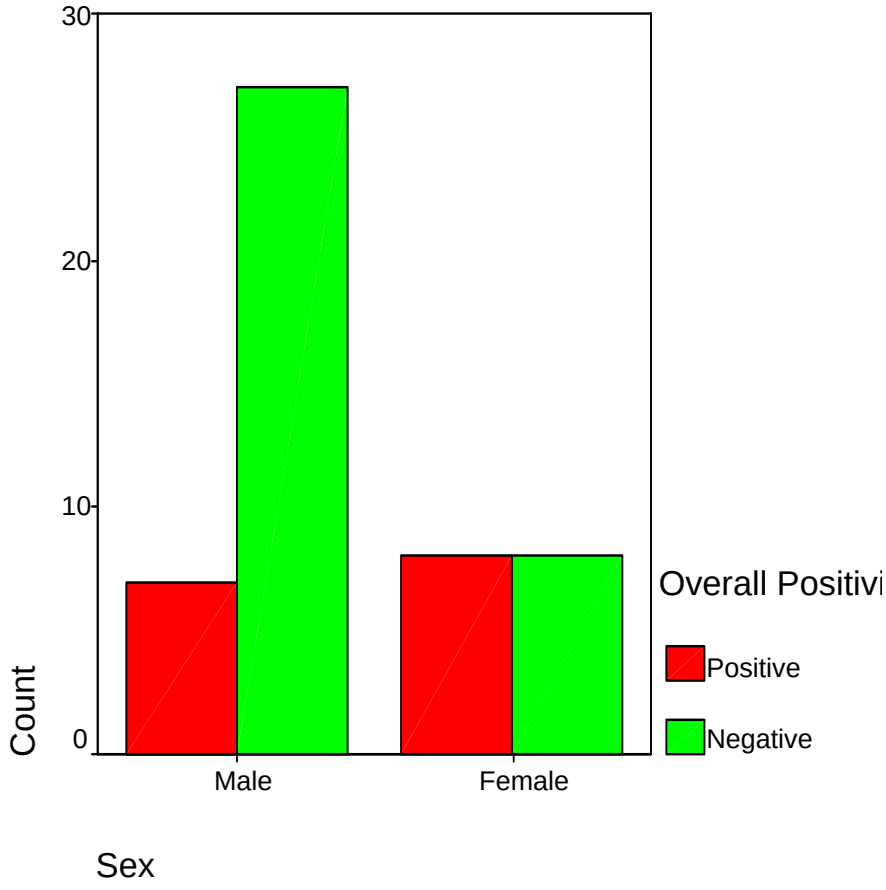
In our study, male patients had high prevalence of MHE than female patients which is statistically significant.

Sex * Overall Positivity

Crosstab

			Overall Positivity		Total	P value
			Negative	Positive		
Sex	Male	Count	7	27	34	< .010 (highly significant)
		% within Sex	20.6%	79.4%	100.0%	
		% within Overall Positivity	46.7%	77.1%	68.0%	
	Female	Count	8	8	16	
		% within Sex	50.0%	50.0%	100.0%	
		% within Overall Positivity	53.3%	22.9%	32.0%	
Total		Count	15	35	50	
		% within Sex	30.0%	70.0%	100.0%	
		% within Overall Positivity	100.0%	100.0%	100.0%	

Highly significant at 1% level

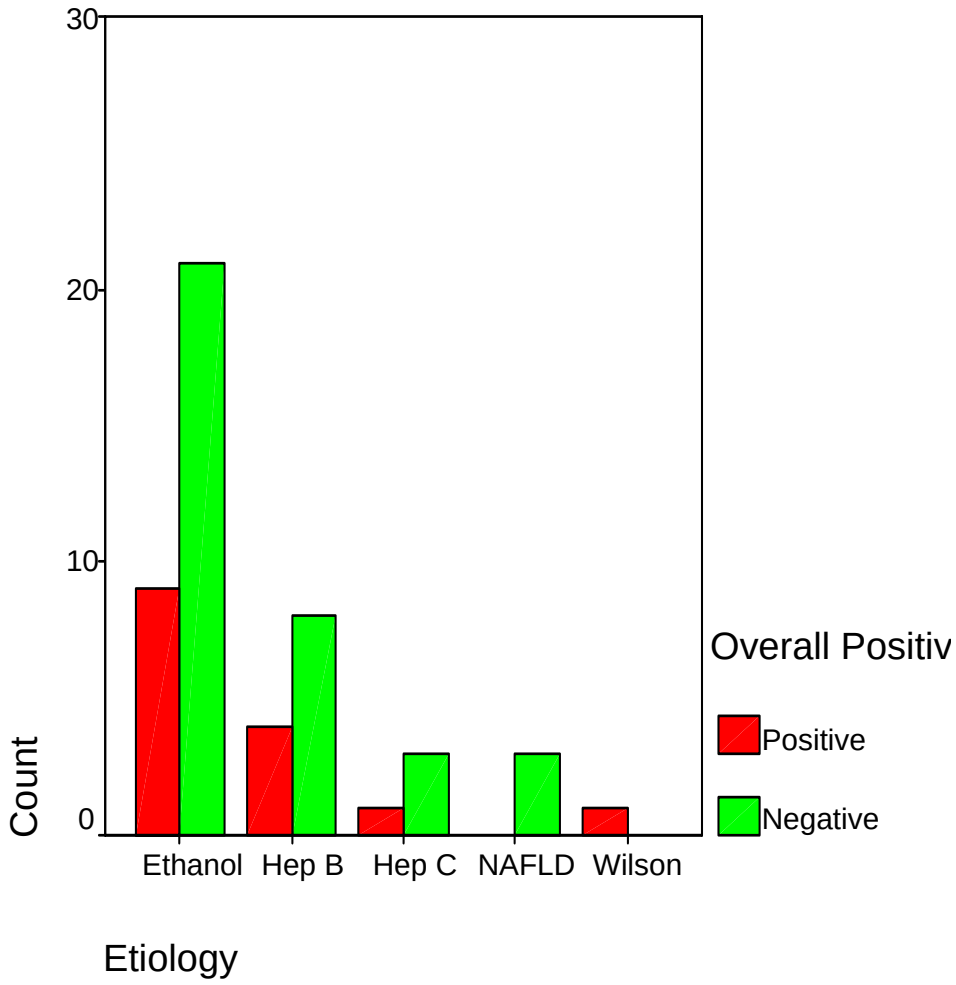

30
20
10
0
Count
Male
Female
Sex
Overall Positivi
Positive
Negative

Etiology * Overall Positivity

Crosstab

			Overall Positivity		
			Negative	**Positive**	**Total**
Etiology	Ethanol	Count	9	21	30
		% within Etiology	30.0%	70.0%	100.0%
		% within Overall Positivity	60.0%	60.0%	60.0%
	Hep B	Count	4	8	12
		% within Etiology	33.3%	66.7%	100.0%
		% within Overall Positivity	26.7%	22.9%	24.0%
	Hep C	Count	1	3	4
		% within Etiology	25.0%	75.0%	100.0%
		% within Overall Positivity	6.7%	8.6%	8.0%
	NAFLD	Count	0	3	3
		% within Etiology	.0%	100.0%	100.0%
		% within Overall Positivity	.0%	8.6%	6.0%

	Wilson	Count	1	0	1
		% within Etiology	100.0%	.0%	100.0%
		% within Overall Positivity	6.7%	.0%	2.0%
Total		Count	15	35	50
		% within Etiology	30.0%	70.0%	100.0%
		% within Overall Positivity	100.0%	100.0%	100.0%


30
20
10
0
Count
Ethanol
Hep B
Hep C
NAFLD
Wilson
Etiology
Overall Positiv
Positive
Negative

In our study, H. pylori infection was found in 30 patients(60%) out of 50 patients. In patients with MHE, 26 patients (74%) had H.pylori infection, whereas only 4 patients (26%) had H.pylori infection in non MHE group which is statistically highly significant.

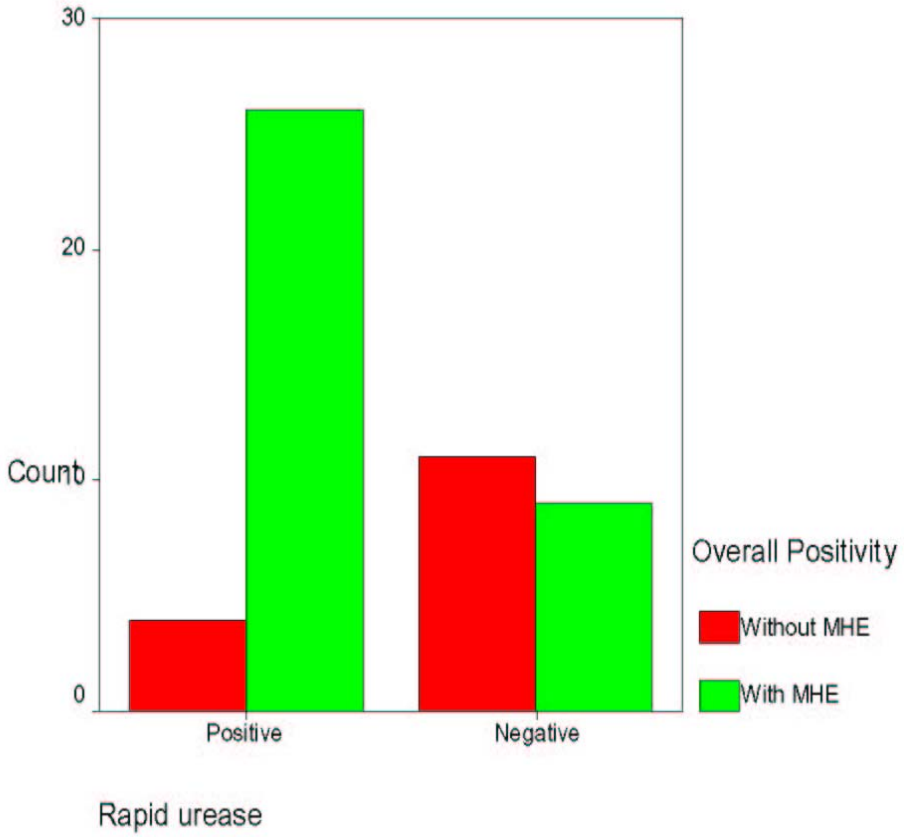
	MHE - POSITIVE	**MHE - NEGATIVE**
H.Pylori - positive	26	4
H.Pylori - negative	9	11

Rapid urease * Overall Positivity

Crosstab

			Overall Positivity		Total	P value
			Negative	Positive		
Rapid urease	Positive	Count	4	26	30	
		% within Rapid urease	13.3%	86.7%	100.0%	
		% within Overall Positivity	26.7%	74.3%	60.0%	<.010 (highly significant
	Negative	Count	11	9	20	
		% within Rapid urease	55.0%	45.0%	100.0%	
		% within Overall Positivity	73.3%	25.7%	40.0%	
Total		Count	15	35	50	
		% within Rapid urease	30.0%	70.0%	100.0%	
		% within Overall Positivity	100.0%	100.0%	100.0%	

Highly significant at 1% level


30
20
10
0
Count
Positive
Negative
Rapid urease
Overall Positivity
Without MHE
With MHE

DISCUSSION

Minimal hepatic encephalopathy impairs daily function and patient's quality of life. Patients with minimal hepatic encephalopathy have difficulties with attention, working memory and response inhibition which is associated with impairment in driving. Patients with MHE are more prone for motor vehicle accidents. Hence, diagnosing and treating MHE is mandatory to avoid morbidity and mortality.

The impact of minimal hepatic encephalopathy on daily life is enormous. Several studies that looked at the quality of life in patients with minimal hepatic encephalopathy showed that patients with MHE have poor quality of life.[59] Schomerus et al also reported that patients with minimal hepatic encephalopathy, do not have regular employment compared to patients without MHE.

In our study the incidence of MHE in asymptomatic cirrhotic patients is 70%. The incidence of MHE has been reported to vary from 22% to 75% in various studies. Sharma et al reported a incidence rate of 41% in asymptomatic cirrhotic patients.[60].

Our study has higher incidence rate than this study. The reason for the large variation is due to the variability in diagnostic criteria. Defining the cut-offs for these neuropsychological tests on the basis of age and education can reduce the variations in incidence rates.

In our study five tests were performed in all patients. Age matched controls were taken and diagnosis of MHE was made if there is more than 2 standard deviation in results compared to controls in two or more psychometric tests.[60]

Most of the studies done in patients with minimal hepatic encephalopathy revealed no sex preponderance. Both males and females are equally affected. In a study done by Agarwal et al,[46] no significant relationship was found between males and females whereas in our study male patients were more prone for minimal hepatic encephalopathy.

Out of 34 male patients, 27 patients had minimal hepatic encephalopathy which is statistically significant at 5%level. This relationship doesn't correlate well with most of the studies.

The most common etiology for cirrhosis in our study is ethanol followed by hepatitis B and hepatitis C. Most of the studies don't show any relationship with etiology and MHE. Our study also doesn't show any relationship with statistical significance.

In our study, thepresence of MHE had no significant relationship with age and CTP score. It is comparable with most studies which also revealed the same.

Hyperammonemia is the widely studied etiological factor in the pathogenesis of hepatic encephalopathy. About 50% of ammonia is produced by intestinal bacteria and rest of them from dietary protein and glutamine. H.pylori is rich in enzyme urease and produces ammonia from urea.

Although the amount of ammonia produced in small, it is postulated in the pathogenesis of minimal hepatic encephalopathy.[61] In a study done by Avinashagarwal et al, lucknow, patients with MHE had high ammonia levels than patients without MHE.

Moreover patients with MHE and H.pylori infection have high ammonia levels than patients with MHE and H.pylori infection. This finding shows a possible association between H.pylori and minimal hepatic encephalopathy.

In our study the prevalance of H.pylori is 60%. The prevalance of H.pylori infection is increased in patients with minimal hepatic encephalopathy (74%) whereas the incidence is only 26% in the non MHE group which is statistically very significant.

These results were comparable to a hospital based study done in lucknow, uttarpradash by agarwal et al. In that study H.pylori infection was found in 22 of 35 patients with minimal hepatic encephalopathy (63%) whereas only 11 patients of 30 patients without MHE had H pylori infection (30%).

Most of the studies reported increased prevalence with raised ammonia levels in patients with MHE. Moreover avinash et al also reported a reduction in blood ammonia levels and normalization of psychometric tests after treatment with anti H.pylori drugs.

Hence we conclude that prevalence of H.pylori is higher in patients with minimal hepatic encephalopathy and further studies are needed to prove a definitive causative role in the pathogenesis of minimal hepatic encephalopathy.

CONCLUSION

1. This study shows the high incidence of minimal hepatic encephalopathy in asymptomatic cirrhotic patients.

2. This study proves that the prevalence of H.pylori is markedly high in patients with minimal hepatic encephalopathy.

BIBLOGRAPHY

1. Voight M, Conn H. Hepatic encephalopathy. In: Robson SC, Trey C, Kirsch RE (editors). Diagnosis and management of liver disease. Chapman & Hall, London, p. 140–147, Chapter 13.

2. Adams RD, Foley JM. The neurological changes in the more common types of severe liver disease.*Trans Am NeurolAssoc* 1949;74:217–19.

3. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy – definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002;35(3):716–21.

4. Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic ncephalopathy. *J Hepatol* 2001;34(5):768–73.

5. Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology* 1977;72(4 Pt 1):573–83.

6. Montagnese S, Amodio P, Morgan MY. Methods for diagnosing hepatic encephalopathy in patients with cirrhosis: a multidimensional approach. *Metab Brain Dis* 2004;19(3–4):281–312.

7. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. *J. Gastroenterol. Hepatol.*2001; **16**: 531–5.

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

9. Schomerus H, Hamster W. Quality of life in cirrhotics with minimal hepatic encephalopathy. *Metab.Brain.Dis.* 2001; **16**: 37–41.

10. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology*2007; **45**: 549–59.

11. Schomerus H, Hamster W, Blunck H, Reinhard U, Mayer K, Dolle W. Latent portasystemic encephalopathy. I. Nature of cerebral functional defects and their effect on fitness to drive. *Dig. Dis. Sci.* 1981; **26**: 622–30.

12. Watanabe A, Tuchida T, Yata Y, Kuwabara Y. Evaluation of neuropsychological function in patients with liver cirrhosis with special reference to their driving ability. *Metab.Brain.Dis.* 1995; **10**: 239–48.

13. Gabuzda GJ Jr, Phillips GB, Davidson CS. Reversible toxic manifestations in patients with cirrhosis of the liver givencation-exchange resins. *N Engl J Med* 1952;246(4):124–30.

14. Albrecht J, Sonnewald U, Waagepertersen HS, et al: Glutamine in the central nervous system: Function and dysfunction. *Front Biosci* 2007; 12:332-43.

15. Lockwood AH, McDonald JM, Reiman RE *et al*. The dynamics of ammonia metabolism in man.Effects of liver disease and hyperammonemia.*J. Clin. Invest.* 1979; **63**: 449–60.

16. Cordoba J, Alonso J, Rovira A *et al*. The development of low-grade cerebral edema in cirrhosis is supported by the evolution of (1)H-magnetic resonance abnormalities after liver transplantation. *J.Hepatol.* 2001; **35**: 598–604.

17. Shawcross DL, Davies NA, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological

effects of induced hyperammonemia in cirrhosis. *J. Hepatol.* 2004; **40**: 247–54.

18. Shawcorss DL, Wright G, OldeDamink SWM, Jalan R. Role of ammonia and inflammation in minimal hepatic encephalopathy. *Metab.Brain.Dis.* 2007; **22**: 125–38.

19. Duchini A, Govindarajan S, Santucci M, Zampi G, Hofman FM. Effects of tumor necrosis factor-alpha and interleukin-6 on fluid-phase permeability and ammonia diffusion in CNS-derived endothelial cells. *J Investig Med* 1996;44(8):474–82.

20. Liu Q, Duon ZP, Ha DK *et al*. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Heptology*2004; **39**: 1441–9.

21. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. *Am. J. Gastroenterol.*2001; **96**: 2718–23.

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

23. Weissenborn K, Ennen JC, Schomerus H, Ruckert N, Hecker H. Neuropsychological characterization of hepatic encephalopathy. *J Hepatol* 2001;34(5):768–73.

24. Ortiz M, Co´rdoba J, Doval E, et al. Development of a clinical hepatic encephalopathy staging scale. Aliment PharmacolTher 2007;26(6):859–67.

25. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35:716–21.

26. Riggio O, Ridola L, Pasquale C, et al. A simplified psychometric evaluation for the diagnosis of minimal hepatic encephalopathy.ClinGastroenterolHepatol 2011;9: 613–616.e1.

27. Randolph C. *The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).* San Antonio: The Psychological Corporation,1998.

28. Sotil EU, Gottstein J, Ayala E, Randolph C, Blei AT. Impact of preoperative overt hepatic encephalopathy on neurocognitive function after liver transplantation.*Liver Transpl*2009;15(2):184–92.

29. Iduru S, Mullen KD. The demise of the pencil? New computer assisted tests for minimal hepatic encephalopathy. *Gastroenterology* 2008;135(5):1455–6.

30. Schiff S, Vallesi A, Mapelli D, et al. Impairment of response inhibition precedes motor alteration in the early stage of liver cirrhosis: a behavioral and electrophysiological study. Metab Brain Dis 2005;20:381–92.

31. Bajaj JS, Saeian K, Verber MD, et al. Inhibitory control test is a simple method to diagnose minimal hepatic encephalopathy and predict development of overt hepatic encephalopathy. *Am J Gastroenterol* 2007;102(4):754–60.

32. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. *Hepatology*2002;35(2):357–66.

33. Marchetti P, D'Avanzo C, Orsato R, et al. Electroencephalography alterations in patients with cirrhosis. Gastroenterology 2011;141:1680–9.

34. Morgan MY, Alonso M, Stanger LC. Lactilol and lactulose for treatment of subclinical HE in cirrhotic patients.*J. Hepatol.* 1989; **8**: 208–17.

35. Kale RA, Gupta RK, Saraswat VA *et al*. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. *Hepatology*2006; **43**: 698–706.

36. Bajaj JS, Saeian K, Christensen KM *et al*. Probiotic yogurt for the treatment of minimal hepatic encephalopathy. *Am. J. Gastroenterol.* 2008; **103**: 1707–15.

37. Sharma P, Sharma BC, Puri V, Sarin SK. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. *Eur. J. Gastroenterol. Hepatol.*2008; **20**: 506–11.

38. Mittal VV, Sharma P, Sharma BC, Sarin S. Treatment of minimal hepatic encephalopathy: A randomised controlled trial comparing lactulose, probiotics and l-ornithine l-aspartate with placebo. *Hepatology*2009; **50**(Suppl): 471A.

39. Ahmad I , Khan AA , Alam A *et al.* L - ornithine - L – aspartate infusion efficacy in hepatic encephalopathy . *J. Coll.Physicians Surg. Pak.* 2008 ;**18** : 684 – 687 .

40. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole.*Gut* 1982;23(1):1–7.

41. Mullen K, Prakash R. Rifaximin for the treatment of hepatic encephalopathy. *Expert Rev GastroenterolHepatol*2010;4(6): 665–77.

42. Amieva MR, El-Omar EM: Host-bacterial interactions in Helicobacter pylori infection. *Gastroenterology* 2008; 134:306-23.

43. Brown LM: Helicobacter pylori: Epidemiology and routes of transmission. *Epidemiol Rev* 2000; 22:283-97.

44. Kawakubo M, Ito Y, Okimura Y, et al: Natural antibiotic function of a human gastric mucin against Helicobacter pylori infection. *Science* 2004; 305:1003-6.

45. Goodman KJ, Joyce SL, Ismond KP: Extragastric diseases associated with Helicobacter pylori. Current Gastroenterology Rep 2006; 17:71-7.

46. Role of Helicobacter pylori infection in the pathogenesis of minimal hepatic encephalopathy and effect of its eradication AvinashAgrawal&Alok Gupta & Mam Chandra &SciddharthaKoowar 18 March 2011 Indian Society of Gastroenterology 2011

47. Versalovic J: Helicobacter pylori. Pathology and diagnostic strategies.*Am J ClinPathol* 2003; 119:403-12.

48. el-Zimaity HM: Accurate diagnosis of Helicobacter pylori with biopsy. *GastroenterolClin North Am* 2000; 29:863-9.

49. Wright CL, Kelly JK: The use of routine special stains for upper gastrointestinal biopsies. *Am J SurgPathol* 2006; 30:357-61.

50. Vakil N, Megraud F: Eradication therapy for Helicobacter pylori. *Gastroenterology* 2007; 133:985-1001.

51. Chey WD, Wong BC: American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol* 2007; 102:1808-25

52. Jodlowski TZ, Lam S, Ashby CR: Emerging therapies for the treatment of Helicobacter pylori infections. *Ann Pharmacother* 2008; 42:1621-39.

53. Peura DA: *Treatment of Helicobacter pylori infection*. In: Wolfe MM, ed. *Therapy of digestive disorders*, Philadelphia: Elsevier; 2006:277

54. Malfertheiner P, Megraud F, O'Morain C, et al: Current concepts in the management of Helicobacter pylori infection: The Maastricht III Consensus Report. *Gut* 2007; 56:772-81.

55. Laine L, Hunt R, El-Zimaity H, et al: Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of Helicobacter pylori in duodenal ulcer patients: A prospective, randomized, multicenter, North American trial. *Am J Gastroenterol* 2003; 98:562-7.

56. Lara LF, Cisneros G, Gurney M, et al: One-day quadruple therapy compared with 7-day triple therapy for Helicobacter pylori infection. *Arch Intern Med* 2003; 163:2079-84

57. Kearney DJ: Retreatment of Helicobacter pylori infection after initial treatment failure. *Am J Gastroenterol* 2001; 96:1335-9.

58. Osato MS, Reddy R, Reddy SG, et al: Pattern of primary resistance of Helicobacter pylori to metronidazole or clarithromycin in the United States. *Arch Intern Med* 2001; 161:1217-20.

59. **Groeneweg M**, Quero JC, De Bruijn I, Hartmann IJ,Essink-bot ML, Hop WC,Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology*1998; **28**: 45-49.

60. Praveen sharma- Review article – Minimal hepatic encephalopathy –JAPI Nov 2009 Vol 57.

61. Jahangir liaquat ,ifthikharkazi – H.pylori and hepatic encephalopathy.Professional Med J Jan-Feb 2012;19(1): 063-067.

PROFORMA

NAME

AGE

SEX

IP NO

SOCIO ECONOMIC STATUS

ADDRESS

CHIEF COMPLAINTS

Abdominal pain

Abdominal distension

Hemetemesis

Jaundice

Melena

PAST HISTORY

Diabetes Mellitus

Hypertension

H/O any neurological illness

Drug History

PERSONAL HISTORY

ALCOHOL/SMOKING

GENERAL EXAMINATION

SIGNS OF LIVER CELL FAILURE

BP

ANAEMIA

JAUNDICE

FLAPPING TREMORS

HEPATOMEGALY

ASCITES

PER RECTAL EXAMINATION

PSYCHOMETRIC TESTS

Number Connection Test A

Number connection Test B

Line tracing test

Serial dotting

Digit symbol test

INVESTIGATIONS

TC DC HB% Motion Occult Blood

LIVER FUNCTION TEST S.Bilirubin T D

SGOT SGPT

SAP

Serum Proteins

BLOOD SUGAR F PP

VIRAL MARKERS: HBsAg and Anti HCV

USG ABDOMEN

UPPER G I ENDOSCOPY WITH ANTRAL BIOPSY

RAPID UREASE TEST

S NO	Name	Age	Sex	Etiology	NCT_A	NCT_B	Line tracing	Serial dotting	Digit symbol	Rapid urease	CTP
1	Neelakandan	38	m	Ethanol	225 sec	360sec	230sec	220sec	9	pos	B
2	Suriya	39	f	Hep c	70 sec	140 sec	80 sec	60 sec	24	neg	A
3	Rathnam	58	f	Hep B	55 sec	110 sec	95 sec	75 sec	22	Pos	B
4	Dhanasekeran	43	m	Ethanol	195 sec	255 sec	165 sec	190 sec	6	pos	A
5	Sathyam	46	m	Hep B	195 sec	270 sec	250 sec	250 sec	8	pos	B
6	Mariammal	52	f	Ethanol	75 sec	120 sec	60 sec	115 sec	20	neg	A
7	Kuppusamy	55	m	Ethanol	310 sec	340 sec	265 sec	175 sec	7	pos	B
8	Chandran	58	m	Ethanol	70 sec	120sec	75sec	75 sec	22	neg	A
9	Hameed	49	m	Ethanol	80 sec	135 sec	90 sec	80 sec	17	pos	A
10	Vimal	39	m	Hep C	210 sec	225 sec	175 sec	195 sec	6	neg	B
11	Akilan	58	m	Ethanol	190 sec	310 sec	300 sec	165 sec	7	pos	A
12	Saravanan	44	m	Hep C	255 sec	330 sec	190 sec	250 sec	7	pos	B
13	Arun	38	m	Hep B	235 sec	265 sec	250 sec	310 sec	4	pos	A
14	Subash	36	m	NAFLD	190 sec	310 sec	175 sec	230 sec	7	neg	B
15	Harichandran	45	m	Ethanol	280 sec	315 sec	310 sec	225 sec	8	neg	B
16	Kannammal	50	F	Hep B	55 sec	100 sec	120 sec	75 sec	20	neg	A
17	Fathima	56	F	Ethanol	115 sec	220 sec	180 sec	225 sec	8	pos	A
18	Ramesh	39	m	Ethanol	160 sec	305 sec	250 sec	145 sec	6	pos	B
19	kalinga	46	m	Ethanol	55 sec	115 sec	80 sec	60 sec	23	neg	B
20	Azmal	42	m	Hep B	75 sec	255 sec	135 sec	225 sec	12	pos	B
21	Pichai	60	m	Ethanol	235 sec	255 sec	255 sec	315 sec	10	pos	B
22	Sridhar	50	m	Hep B	130 sec	250 sec	175 sec	175 sec	7	neg	C
23	Mala	45	f	Hep B	135 sec	315 sec	115 sec	205 sec	6	pos	B
24	Parvathy	46	F	Ethanol	55 sec	115 sec	60 sec	75 sec	24	neg	A
25	Kasi	52	M	Hep B	175 sec	285 sec	225 sec	225 sec	7	pos	A
26	Kuppan	60	m	Ethanol	240 sec	360 sec	250 sec	300 sec	10	pos	A
27	Murali	42	M	Ethanol	145 sec	295 sec	250 sec	255 sec	10	neg	A

28	Ravi	54	M	Ethanol	195 sec	290 sec	190 sec	200 sec	8	neg	A
29	Gopal	47	m	Ethanol	45 sec	120 sec	70 sec	65 sec	25	neg	A
30	Mani	50	m	Ethanol	190 sec	280 sec	215 sec	265 sec	5	pos	C
31	Babu	42	m	Hep C	250 sec	310 sec	300 sec	250 sec	12	pos	B
32	Seker	48	m	Ethanol	70 sec	105 sec	55 sec	65 sec	26	neg	B
33	Velankanni	42	f	Ethanol	200 sec	235 sec	190 sec	255 sec	8	pos	B
34	Saraswathy	49	f	wilson	65 sec	120 sec	55 sec	65 sec	22	neg	A
35	John	36	m	Ethanol	60sec	100 sec	60 sec	55 sec	22	neg	A
36	Vijayalakshmi	46	f	NAFLD	160 sec	250 sec	180 sec	165 sec	10	pos	A
37	Joseph	56	m	Ethanol	175 sec	235 sec	225 sec	235 sec	8	pos	C
38	meiyammai	50	f	Hep B	115 sec	235 sec	175 sec	250 sec	7	pos	B
39	Selvi	47	F	Hep B	80 sec	115 sec	125 sec	85 sec	22	neg	B
40	Pramoth kumar	41	m	Ethanol	270 sec	350 sec	200 sec	250 sec	5	pos	A
41	Raja	42	m	Ethanol	215 sec	250 sec	195 sec	135 sec	5	neg	B
42	Hussain	52	m	Ethanol	250 sec	315 sec	240 sec	180 min	12	pos	B
43	kamalam	50	f	Ethanol	150 sec	310 sec	250 sec	195 sec	12	pos	B
44	Jenas	49	f	NAFLD	185 sec	350 sec	170 sec	190 sec	12	pos	A
45	Vijayakumar	34	m	Hep B	175 sec	280 sec	175 sec	255 sec	5	pos	B
46	Karthick	48	m	Ethanol	230 sec	255 sec	235 sec	225 sec	13	neg	B
47	Mani	47	m	Ethanol	270 sec	310 sec	195 sec	165 sec	7	pos	A
48	Ramathal	51	f	Hep B	180 sec	285 sec	255 sec	160 sec	6	neg	B
49	Vimala	47	f	Ethanol	85 sec	115 sec	110 sec	85 sec	18	pos	B
50	Chidambaram	49	m	Ethanol	235 sec	285 sec	310 sec	115 sec	10	pos	A

S.NO	Name	age	sex	NCT-A	NCT-B	Line tracing	serial dotting	digit symbol
1	Rajendran	34	m	30 sec	100 sec	82 sec	60 sec	26
2	shankar	37	m	57 sec	165 sec	70 sec	80 sec	20
3	John	56	m	55 sec	150 sec	55 sec	100 sec	23
4	suresh	39	m	55 sec	165 sec	75 sec	60 sec	17
5	balaji	34	m	95 sec	135 sec	130 sec	105 sec	16
6	geetha	38	f	35 sec	80 sec	75 sec	50 sec	26
7	Praveen	32	m	44 sec	105 sec	150 sec	70 sec	24
8	kamaleswar	33	m	45 sec	115 sec	110 sec	75 sec	17
9	priya	32	f	65 sec	80 sec	100 sec	50 sec	25
10	vijayakumar	43	m	45 sec	75 sec	105 sec	65 sec	23
11	munusamy	42	m	40 sec	60 sec	95 sec	50 sec	20
12	madhu	39	m	55 s ec	55 sec	85 sec	90 sec	17
13	dhanasekar	45	m	65 sec	120 sec	80 sec	60 sec	15
14	dhakshinamoo	38	m	65 sec	130 sec	105 sec	65 sec	18
15	jaya	44	f	90 sec	140 sec	115 sec	75 sec	25
16	gopal	48	m	55 sec	115 sec	80 sec	55 sec	21
17	tamilanban	43	m	50 sec	90 sec	85 sec	80 sec	20
18	janani	48	f	60 sec	90 sec	110 sec	85 sec	17
19	rehman	55	m	45 sec	125 sec	115 sec	55 sec	18
20	mariammal	39	f	65 sec	135 sec	120 sec	100 sec	16
21	malliga	46	f	55 sec	110 sec	75 sec	55 sec	27
22	kannan	48	m	60 sec	105 sec	55 sec	65 sec	20
23	sundaram	43	m	45 sec	100 sec	65 sec	50 sec	22
24	abirami	48	f	35 sec	85 sec	75 sec	55 sec	28
25	shahul	53	m	65 sec	120 sec	85 sec	65 sec	19
26	kamalakannan	46	m	55 sec	135 sec	95 sec	75 sec	20
27	murugan	48	m	75 sec	145 sec	105 sec	80 sec	21
28	haribabu	42	m	100 sec	160 sec	115 sec	105 sec	18
29	latha	39	f	60 sec	100 sec	60 sec	55 sec	24
30	arunkumar	52	m	80 sec	120 sec	75 sec	85 sec	17