EVALUATION OF PREVALENCE OF MINIMAL HEPATICL ENCAPHALOPATHY IN PATIENTS WITH COMPENSATED CIRRHOSIS

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CERTIFICATE

This is to certify that the Dissertation entitled **"EVALUATION OF THE PREVALENCE OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH COMPENSATED CIRRHOSIS"** here with submitted by Dr. T.YOGANANDH, Post graduate in General Medicine, Coimbatore Medical College to the Tamilnadu Dr.M.G.R Medical University is a record of a bonafide research work carried out by him under my guidance and supervision from June 2008 to May 2009.

Dr. VEERAKESARI, MD
Professor & Unit chief,
Department of Medicine.

Dr. UMAKANTHAN, MD
Professor & Head,
Department of Medicine.

DEAN

Coimbatore Medical College

Coimbatore

DECLARATION

I solemnly declare that the Dissertation titled "EVALUATION OF THE PREVALENCE OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH COMPENSATED CIRRHOSIS," was done by me at Coimbatore Medical College and Hospital during the period from June '08 to July '09 under the guidance and supervision of Prof. Dr. Veerakesari,M.D.

This dissertation is submitted to the Tamil Nadu Dr. M.G.R Medical University towards the partial fulfillment of the requirement for the award of MD Degree (Branch I) in General Medicine.

Place : Coimbatore

Date : **Dr.T.YOGANANDH**

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CONTENTS

INTRODUCTION

1. INTRODUCTION

Hepatic encephalopathy(HE) is a leading cause of morbidity and mortality in patients with Cirrhosis of liver and can its manifested with subtle alterations in neurocognitive functions or with depressed level of consciousness.[1,2]

Hepatic encephalopathy is a leading cause of morbidity and mortality in patients with cirrhosis and other porto-systemic shunting of intestinal blood[4]

Minimal Hepatic Encephalopathy (MHE) is now well established phenomenon and is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects but with a normal neurological examination.[3]

Identification of MHE is now possible with easily available neuropsychiatric methods and treatment should be promptly instituted to prevent further deterioration.

AIM OF THE STUDY

2. AIM OF THE STUDY

The objectives of this study are:

1. To evaluate the prevalence of cognitive and performance impairment in patients with compensated cirrhosis of liver.
2. To evaluate the Electro Encephalographic abnormalities as a marker of cerebral cortical involvement in such patients using EEG.
3. To assess the prevalence of Minimal Hepatic Encephalopathy in compensated cirrhotics by using Psychometric testing and EEG.

REVIEW OF LITERATURE

3. REVIEW OF LITERATURE

3.1 DEFINITION

Hepatic encephalopathy (HE) is a neuropsychiatric disorder that may accompany either acute or chronic liver disease. It is defined as a disturbance of central nervous system function due to hepatic insufficiency and includes a large spectrum of clinical manifestations such as decreased intellectual function, personality disorders, alterations in the level of consciousness and neuromuscular dysfunctions.[5]

HE can be classified into 3 major clinical types:

a. HE associated with acute liver failure.

b. HE associated with portal systemic bypass and no intrinsic hepatocellular disease.

c. HE associated with cirrhosis and portal hypertension/ or portal-systemic shunts.

HE associated with cirrhosis and portal hypertension/ or portal systemic shunts is classified further as

I. Episodic HE

II. Persistent HE

III. Minimal -or subclinical- HE (MHE)[6]

MHE is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects with a normal neurological examination.

3.2 CIRRHOSIS – AN OVERVIEW

In order to understand Hepatic Encephalopathy and its antecedent Minimal Hepatic Encephalopathy an understanding of cirrhosis and other complications is needed.

3.2.1 DEFINITION

Cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[16]

3.2.2 EPIDEMIOLOGY

Cirrhosis and chronic liver disease accounts for 26,000 to 35,000 deaths per annum in India and 2000 additional cases of Fulminant Hepatic Failure (FHF) die every year. FHF can be caused by drugs (acetaminophen), Post Infectious (Hepatitis A & B), Wilson disease and various other common causes. Cryptogenic cases account for about a

third of these cases of FHF. The mortality is very high (50% - 80%) unless salvaged by liver transplant.

3.2.3 ETIOLOGY

In India, causes of cirrhosis vary from that of Western World.

While in the countries like the US Hepatitis is a leading cause, alcohol remains common in India.

- Alcoholic Liver disease (35%)
- Post-Infectious causes (30%)
- Cryptogenic causes (18%)
- Post hepatic and biliary causes (8%)
- Miscellaneous (9%)

Cirrhosis is said to be compensated when manifestations of liver failure are absent. Those patients with signs of liver cell failure or its complications are classified as decompensated cirrhotics

Miscellaneous causes of chronic liver disease and cirrhosis

- Autoimmune hepatitis
- Primary biliary cirrhosis

- Secondary biliary cirrhosis (associated with chronic extrahepatic bile duct obstruction)
- Primary sclerosing cholangitis
- Hemochromatosis
- Wilson disease
- Alpha-1 antitrypsin deficiency
- Granulomatous disease (eg, sarcoidosis)
- Type IV glycogen storage disease
- Drug-induced liver disease (eg, methotrexate, alpha methyldopa, amiodarone)
- Venous outflow obstruction (eg, Budd-Chiari syndrome, veno-occlusive disease)
- Chronic right-sided heart failure
- Tricuspid regurgitation

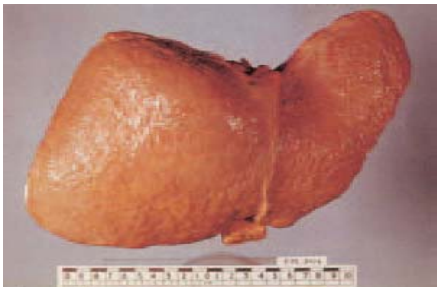
3.2.4 PATHOPHYSIOLOGY OF CIRRHOSIS

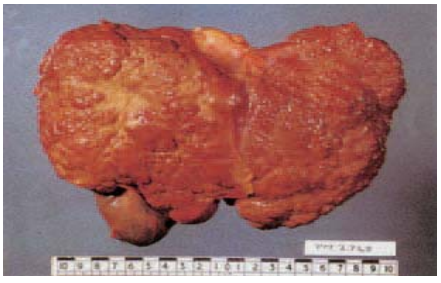
Normal liver extracellular matrix, the normal scaffolding for hepatocytes, is composed of collagens (especially types I, III, and V), glycoproteins, and proteoglycans. The development of hepatic fibrosis reflects an alteration in the normally balanced processes of extracellular matrix production and degradation. Whenever there is any injury to the

hepatic cells by way of toxins, alcohol etc, there are characteristic changes.

Stellate cells, located in the perisinusoidal space, are essential for the production of extracellular matrix. Paracrine factors may be released by hepatocytes, Kupffer cells, and sinusoidal endothelium following liver injury. As an example, increased levels of the cytokine transforming growth factor beta1 (TGF-beta1) is observed in patients with cirrhosis. TGF-beta1, in turn, stimulates activated stellate cells to produce type I collagen.

Future drug strategies to prevent fibrosis may focus on reducing hepatic inflammation, inhibiting stellate cell activation, inhibiting the fibrogenic activities of stellate cells, and stimulating matrix degradation.

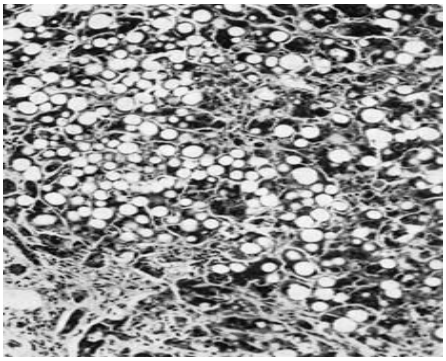

The small finely nodular liver of micronodular cirrhosis


Macronodular cirrhosis

3.2.5 HISTOLOGY

The final and irreversible form of liver disease usually evolves slowly and insidiously. At first the cirrhotic liver is yellow-tan, fatty, and enlarged, usually weighing over 2 kg. Over the span of years it is transformed into a brown, shrunken, nonfatty organ, sometimes weighing less than 1 kg.

Cirrhosis may develop more rapidly in the setting of alcoholic hepatitis, within 1 to 2 years. Regenerative activity of entrapped parenchymal hepatocytes generates fairly uniformly sized nodules. Since these nodules tend to be less than 0.3 cm in diameter, this pattern of cirrhosis is termed ***micronodular cirrhosis*** (vs. the ***macronodular cirrhosis*** described for viral hepatitis). Scattered larger nodules create a "hobnail" appearance on the surface of the liver. As fibrous septa dissect and surround nodules, the liver becomes more fibrotic, loses fat, and shrinks progressively.



Micronodular cirrhosis. Gross fatty change.

Ischemic necrosis and fibrous obliteration of nodules eventually create broad expanses of tough, pale scar tissue. Bile stasis often develops; Mallory bodies are rarely evident at this stage. Thus, end-stage alcoholic cirrhosis eventually comes to resemble, both macroscopically and microscopically, the cirrhosis developing from viral hepatitis and other causes.

3.2.6 CLINICAL FEATURES

Patients with alcoholic liver disease can present with nonspecific symptoms such as vague right upper quadrant pain, fever, nausea and vomiting, diarrhea, anorexia, and malaise. Alternatively, they may present with more specific complications of chronic liver disease, including ascites, edema, or upper gastrointestinal (GI) hemorrhage. Pruritis is an important manifestation of biliary cirrhosis.

Other clinical manifestations include the development of jaundice or encephalopathy. On physical examination, the liver and spleen may be enlarged, with the liver edge being firm and nodular.[16]

Frequent findings include scleral icterus, palmar erythema, spider angiomas, parotid gland enlargement, digital clubbing, muscle wasting, or the development of edema and ascites.

Men may have decreased body hair and gynaecomastia and testicular atrophy, which may be a consequence of hormonal abnormalities or a direct toxic effect of alcohol on the testes. In women with advanced alcoholic cirrhosis, menstrual irregularities usually occur, and some women may be amenorrheic. These changes are often reversible following cessation of alcohol.

SYMPTOMS:

Jaundice is absent in cirrhosis. It suggests either that the causative agent is still active or hepatic decompensation has occurred indicating further progression of the disease.

Weakness, easy fatigability & tiredness are very common and contribute to the general malaise of cirrhosis, though objective evidence of weakness is unusual. Anorexia is frequently present.

Nausea and vomiting are common and one has to look for remediable cause for these symptoms. Vomitus has to be examined to rule out hemetemisis. Abdominal pain or right hypochondrial pain or discomfort may be present. Tenderness may be localized to lower right ribs.

Abdomen distension is due to ascites. Fluid retention may lead to sacral or ankle edema.Patients may have constipation or diarrhea. Dyspnea may be associated with gross ascites. This can also be due to associated pulmonary fibrosing alveolitis, pulmonary shunting and pulmonary hypertension.

Patients may often complain of nose or oral bleed. This may lead to hepatic encephalopathy. Fever may occur without a cause and patient can be depressed. In Biliary cirrhosis pruritus is seen in approximately 50% of patients at the time of diagnosis and can be debilitating.

3.2.7 PHYSICAL SIGNS

Most patients with cirrhosis look well until the late stage of the disease, when muscle wasting and loss of adipose tissue may become prominent.

Protein-calorie malnutrition is a common complication of chronic liver disease, present in 20% of patients with compensated cirrhosis and more than 60% of those with severe hepatic dysfunction [17]

Pallor may be due to recent UGI bleed or iron deficiency anemia due to chronic blood loss. Macrocytosis (MCV) greater than 95 fl is presumably due to a direct effect of alcohol on bone marrow.

Deficiencies of folate and vitamin B12 contribute to macrocytocis in the malnourished patient. *The combination of a raised MCV and serum g-GT will identify 90% of alcohol-dependent patients.*

Eye signs. Lid retraction and lid lag is significantly increased in patients with cirrhosis compared with a control population[18].However Serum-free thyroxine is not increased.

Parotid gland enlargement and Dupuytren's contracture are seen in some alcoholic patients with cirrhosis. Digital clubbing and hypertrophic osteoarthropathy may complicate cirrhosis, especially biliary cirrhosis. These changes may be due to aggregated platelets, passing peripherally through pulmonary arteriovenous shunts, plugging capillaries and releasing PDGF.[19]

Muscle cramps occur significantly more frequently in cirrhotic patients than in patients without liver disease, and correlate with the presence of ascites and plasma renin activity.[20] Splenomegaly and abdominal wall venous collaterals usually indicate portal hypertension.

Abdominal herniae are common with ascites. They should not be repaired unless life endangering or the cirrhosis is very well compensated. Spider naevi, palmar erythema, paper money skin are also found in cirrhosis (alcoholic). Excessive bleeding and petechiae are found in skin when liver function deteriorates.

Those with hemochromatosis may show widespread melanin pigmentation with localized hyperpigmentation. Vitiligo occurs in autoimmune hepatitits. Dupuytern's contracture and parotid enlargement are seen more commonly in alcoholic cirrhosis. Flapping tremor or asterixis may be observed in patients with hepatic encephalopathy. Kayser Fleischer ring is seen in Wilson's disease and is a potentially treatable condition.

ABDOMINAL SIGNS:

PORTAL HYPERTENSION:

The normal liver has the ability to accommodate large changes in portal blood flow without appreciable alterations in portal pressure. Portal hypertension results from a combination of increased portal venous inflow and increased resistance to portal blood flow.

In cirrhosis, decreased local production of nitric oxide by endothelial cells permits stellate cell contraction, with resulting vasoconstriction of the hepatic sinusoid. Increased local levels of vasoconstricting chemicals, like endothelin, may also contribute to sinusoidal vasoconstriction. The classic sinusoidal cause of portal hypertension is cirrhosis.

MEASUREMENT OF PORTAL HYPERTENSION:

Free Hepatic Vein Pressure (FHVP) is equal to inferior vena caval pressure. FHVP is used as an internal zero reference point. Wedged Hepatic Venous Pressure (WHVP) is measured by inflating a balloon at the catheter tip, thus occluding a hepatic vein branch. Measurement of the WHVP provides a close approximation of portal pressure (PP). Both the WHVP and PP are elevated in patients with sinusoidal portal hypertension, as is observed in cirrhosis.

CONSEQUENCES OF PORTAL HYPERTENSION:

Ascites , Hepatic Encephalopathy

ASCITES:

Ascites is defined as an accumulation of excessive fluid within the peritoneal cavity and may be a complication of both hepatic and nonhepatic diseases. When the gradient between the serum albumin level and the ascitic fluid albumin level is >1.1 g/dL, the cause of the ascites is most likely due to portal hypertension; this is most often in the setting of cirrhosis. When the gradient is <1.1 g/dL, infectious or malignant causes of ascites should be considered.

In exudative ascites, fluid weeps from an inflamed or tumor-laden peritoneum. In general, ascites protein is greater than 2.5 g/dL. Examples included peritoneal carcinomatosis and tuberculous peritonitis.

The role of portal hypertension in the pathogenesis of cirrhotic ascites:

Normally the trans-sinusoidal oncotic gradient is approximately zero. The increased sinusoidal pressure that develops in portal hypertension increases the amount of fluid entering the space of Disse.

The role of renal dysfunction in the pathogenesis of cirrhotic ascites

The peripheral arterial vasodilation hypothesis states that splanchnic arterial vasodilation, driven by high nitric oxide levels, leads to intravascular underfilling. This leads to stimulation of the renin-angiotensin system and the sympathetic nervous system and release of antidiuretic hormone.

Spontaneous bacterial peritonitis

SBP is observed in 15-26% of patients hospitalized with ascites. The syndrome arises most commonly in patients whose low-protein ascites (<1 g/dL) since it contains low levels of complement thereby resulting in decreased opsonic activity. SBP appears to be caused by the translocation of GI tract bacteria across the gut wall and also by the

hematogenous spread of bacteria. The most common causative organisms are *Escherichia coli, Streptococcus pneumoniae, Klebsiella* species, and other gram-negative enteric organisms.

Other complications of massive ascites

Patients with massive ascites may experience abdominal discomfort, depressed appetite, and decreased oral intake. Diaphragmatic elevation and pleural effusion may lead to symptoms of dyspnea. Umbilical and inguinal hernias are common in patients with moderate and massive ascites. Umbilical hernias should not undergo elective repair unless patients are significantly symptomatic or their hernias are irreducible.

INVESTIGATIONS

Heamotology:

Routine blood counts may be normal in cirrhosis especially early in cirrhosis. Mild anemia is common. On blood films target cells may be seen and in rare cases acanthocytes and other features of hemolytic anemia may be seen.

Anemia may result from folate deficiency, hemolysis, or hypersplenism. Thrombocytopenia usually is secondary to hypersplenism

and decreased levels of thrombopoietin. If cholestasis is present it leads to decreased vitamin K absorption, with resulting reduction in hepatic production of factors II, VII, IX, and X.

The White Blood Count tends to fall in patients with cirrhosis, due to hypersplenism. The platelet count is usually low in cirrhotics again due to hypersplenism.

BIOCHEMICAL:

Liver Function Tests:

They are only of limited value in cirrhosis as they may be normal. Aspartate Amino Transferase (AST) and Alanine Amino Transferase (AST) are normal in cirrhosis especially if the causative agent is no longer active or because of effective treatment.

In alcoholics with alcoholic hepatitis and minimal cirrhosis, AST/ALT ratio is usually greater than 2. In most patients, Serum Alkaline Phophatase (SAP) is normal, except in biliary cirrhosis.

The levels of Gamma Glutamyl transferase levels (GGT) may be increased in alcoholic cirrhosis. The serum total bilirubin is usually

normal. An increase in bilirubin without any obvious cause suggests hepatic decompensation. *Low albumin levels are usually due to reduced hepatic synthesis.*

OTHER BIOCHEMICAL TESTS:

Plasma electrolytes are usually abnormal in cirrhosis and requires close monitoring. Hyponatremia is common but hypernatremia is less common and may occur with GI bleeding, use of lactulose and with severe fluid restriction. Serum potassium is usually normal in cirrhosis. But both hypo and hyper kalemia is observed depending upon the type of diuretic therapy instituted.

COMPLICATIONS OF CIRRHOSIS:

The clinical course of patients with advanced cirrhosis is often complicated by a number of important sequelae that can occur regardless of the underlying cause of the liver disease. These include portal hypertension and its consequences of gastroesophageal variceal hemorrhage, splenomegaly, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, and hepatocellular carcinoma.

Table listing complications of cirrhosis

Portal hypertension	Coagulopathy
Gastroesophageal varices	Factor deficiency
Portal hypertensive gastropathy	Fibrinolysis
Splenomegaly, hypersplenism	Thrombocytopenia
Ascites	Bone disease
Spontaneous bacterial peritonitis	Osteopenia
Hepatorenal syndrome	Osteoporosis
Type 1	Osteomalacia
Type 2	Hematologic abnormalities
Hepatic encephalopathy	Anemia
Hepatopulmonary syndrome	Hemolysis
Portopulmonary hypertension	Thrombocytopenia
Malnutrition	Neutropenia

Of these, the major ones are

1. Portal Hypertension and ascites
2. Hepatic Encephalopathy
3. Hepatocellular carcinoma
4. Infections

The minor complications of significance are

1. Fluid and Electrolyte disturbances
2. Anemia and hemolysis
3. Hepatorenal syndrome
4. Hepatopulmonary syndrome
5. Gall stone

PROGNOSIS:

The most common tool for gauging prognosis in cirrhosis is the Child-Turcotte-Pugh (CTP) system. Child and Turcotte first introduced their scoring system in 1964 as a means of predicting the operative mortality associated with portocaval shunt surgery. Pugh's revised system in 1973 substituted albumin for the less specific variable of nutritional status.[24] More recent revisions use the International Normalized Ratio (INR) in addition to prothrombin time.

Child-Turcotte-Pugh Scoring System for Cirrhosis

Clinical variable	**1 point**	**2 points**	**3 points**
Encephalopathy	None	Stages- 1 -2	Stages3-
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
(Bilirubin in PBC			
or PSC (mg/dL)	<4	4-10	>10
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time			
(seconds prolonged			
or INR)	<4 s or INR <1.7	4-6 s or INR 1.7-2.3	>6 s or INR >2.

[Child Class A=5-6 points, Child Class B=7-9 points, Child Class C=10-15 points]

Recent epidemiologic work shows that the CTP score may predict life expectancy in patients with advanced cirrhosis. A CTP score of 10 or greater is associated with a 50% chance of death within 1 year.

2. Cox's Regression Model:

Poor prognosis is associated with

- Prolonged prothrombin time
- Marked ascites
- Gastrointestinal bleed
- Advanced age
- Continuing alcohol consumption
- High serum bilirubin
- Spontaneous bacterial peritonitis
- Ascites

TREATMENT:

Specific medical therapies may be applied to many liver diseases in an effort to diminish symptoms and to prevent or forestall the development of cirrhosis. Examples include prednisone and azathioprine for autoimmune hepatitis, interferon and other antiviral agents for

hepatitis B and C, phlebotomy for hemochromatosis, ursodeoxycholic acid for primary biliary cirrhosis, and trientine and zinc for Wilson disease.

Once cirrhosis develops, treatment is aimed at the management of complications as they arise.

Nutrition

Many patients complain of anorexia, which may be compounded by the direct compression of ascites on the GI tract. Patients frequently benefit from the addition of commonly available liquid and powdered nutritional supplements to the diet. Institution of a low-protein diet in the fear that hepatic encephalopathy might develop may result in development of profound muscle wasting.

Adjunctive therapies

Zinc deficiency commonly is observed in patients with cirrhosis. Treatment with zinc sulfate at 220 mg orally twice daily may improve dysgeusia and can stimulate appetite. Furthermore, zinc is effective in the treatment of muscle cramps and is adjunctive therapy for hepatic encephalopathy.

Pruritus is a common complaint in both cholestatic liver diseases (eg, primary biliary cirrhosis) and in noncholestatic chronic liver diseases (eg, hepatitis C). Serum bile acids and endogenous opioids are more likely to be pruritogens.

Cholestyramine is the mainstay of therapy for the pruritus of liver disease. Patients with severe pruritus may require institution of ultraviolet light therapy or plasmapheresis.

Patients with cirrhosis may develop osteoporosis. Supplementation with calcium and vitamin D is important in patients at high risk for osteoporosis.

HEPATIC ENCEPHALOPATHY

DEFINITION

Hepatic encephalopathy (HE) can be defined as a disturbance in central nervous system (CNS) function due to hepatic insufficiency or portosystemic shunting[25]. This vague definition reflects the existence of a spectrum of neurologic manifestations that develop in association with different liver diseases.

The encephalopathy of cirrhosis has portal-systemic shunting as a component but hepato-cellular dysfunction is also important; various

precipitating factors playing a part. Cerebral Edema is an important feature of acute liver failure, which often manifests with mania.

The experts decided to classify HE into three types – A, B, and C. The most frequent is type C.

Table

Type A HE	associated with **A**cute liver failure
Type B HE	associated with portal-systemic **B**ypass, no intrinsic hepatocellular disease
Type C HE	associated with **C**irrhosis and portal hypertension or portal-systemic shunts:

– Episodic HE: precipitated, spontaneous, recurrent
– Persistent HE: mild, severe, treatment-dependent
- Minimal HE

Patients with HE may have altered brain energy metabolism and increased permeability of the blood-brain barrier. Putative neurotoxins include short-chain fatty acids, mercaptans, false neurotransmitters (eg, tyramine, octopamine, and beta-phenylethanolamines), ammonia, and gamma-aminobutyric acid (GABA).

Table

Types of hepatic encephalopathy

Type of encephalopathy	**% Survival**	**Aetiological factors**
Acute liver failure	20*	Viral hepatitis Alcoholic hepatitis Drug reactions and overdose
Cirrhosis with precipitant	70–80	Diuresis, Hemorrhage Paracentesis, Diarrhea vomiting, surgery Alcoholic excess Sedatives,Infections
Type of encephalopathy	**% Survival**	**Aetiological factors**

Type of encephalopathy	% Survival	Aetiological factors
		Constipation
Chronic portal-systemic encephalopathy	100	Portal-systemic shunting Dietary protein intake & Intestinal bacteria

According to the consensus arrived at the 11th World Congress of Gastroenterology, HE can be classified into 3 major clinical types:

a. HE associated with acute liver failure.

b. HE associated with portal systemic bypass and no intrinsic hepatocellular disease.

c. HE associated with cirrhosis and portal hypertension/ or portalsystemic shunts.

This last type can be divided in 3 subtypes:

I. Episodic HE

II. Persistent HE

III.Minimal -or subclinical- HE (MHE)

The clinical grades of hepatic encephalopathy

I	Mild confusion, euphoria, anxiety or depression Shortened attention span Slowing of ability to perform mental tasks (addition/subtraction) Reversal of sleep rhythm
II	Drowsiness, lethargy, gross deficits in ability to perform mental tasks Obvious personality changes Inappropriate behaviour Intermittent disorientation of time (and place) Lack of sphincter control
III	Somnolent but rousable Persistent disorientation of time and place Pronounced confusion

Unable to perform mental tasks

IV Coma with (IVa) or without (IVb) response to painful stimuli

PATHOGENISIS

Ideally, HE should be discussed in relation to liver abnormalities, neurologic disturbances, and clinical manifestations. However, establishing such relations is difficult. A common pathogenetic notion is that HE is caused by substances which under normal circumstances are efficiently metabolized by the liver. In patients with liver disease, these toxic substances reach the systemic circulation through portosystemic shunting or reduced hepatic clearance and produce deleterious effects on brain function.

Historical hypotheses have ranged from single ***unifying theories***[26] to the notion of HE as a ***multifactorial process***[27]. A unique feature of HE is the abnormality of astrocyte morphology and function. This feature has led to a view that in HE the abnormality in consciousness is the consequence of altered astrocyte–neuronal communications[28].

Alternative views, such as the γ-aminobutyric acid (GABA) theory, explain the spectrum of HE through the direct effect of a toxin on a key aspect of neurologic function[29]. Other paradigms arise from the experimental observation that different toxins (e.g., fatty acids or mercaptans) enhance the negative effects of ammonia on consciousness

(*synergistic theory*). Finally, current views also emphasize differing effects of different toxins at various neurologic levels. For example, manganese appears to be involved in Parkinsonian manifestations but not in decreasing arousal.

At present, the main substances considered to be implicated in the development of HE are ammonia and other intestinal neurotoxins, manganese and the Benzodiazepine- GABA system[1]. However, alterations in neurotransmission are probably the main cause of HE. Ammonia possibly plays a major role in these abnormalities. At present, it is difficult to ascribe changes in other neurotransmission systems that have been detected in HE to the clinical manifestations of this syndrome.

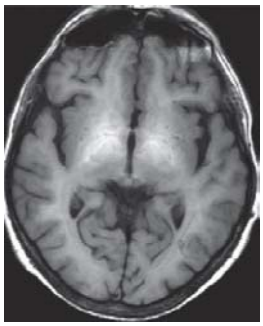
Pathology and Neuroimaging in HE

Although HE is a functional syndrome, the most common pathological finding in patients with advanced or persistent HE is the presence of the so-called Alzheimer's type II astrocytosis because of an increase in intracellular water that is produced by the hyperammonemia.[30]

On magnetic resonance spectroscopy (MRS), the cerebral concentrations of glutamine are high and those of myoinositol low, reflecting the activation of the osmoregulation.

The role of neuroimaging in the study of HE is stressed by the finding of the previously mentioned changes in MRI or MRS. Positron

emission tomography (PET) has also been used in the study of the pathophysiological mechanisms of HE.


MRI showing Globus pallidus hyperintensity in T2 weighted image

The essentially reversible nature of the syndrome with such widespread cerebral changes suggests a metabolic mechanism. However, no single metabolic derangement accounts for hepatic encephalopathy. Several neuroactive toxins, in particular ammonia, and neurotransmitter systems are thought to be involved and inter-relate.

Neurotransmission

Although there are many studies in experimental and human encephalopathy, the overall picture remains complex and in many areas conflicting and controversial. Definitive data are difficult to collect.

Ammonia and glutamine

Ammonia is produced from the breakdown of proteins, amino acids, purines and pyrimidines. About half of the ammonia arising from the intestine is synthesized by bacteria, and the remainder comes from

dietary protein and glutamine. The liver normally converts ammonia to urea and glutamine through the urea cycle.

In hepatic encephalopathy blood ammonia levels are elevated in 90% of patients. Brain levels of ammonia are also increased. Encephalopathy can be reproduced in some patients by oral ammonium salts.

Hyperammonaemia *per se* is associated with decreased excitatory neurotransmission. Ammonia intoxication leads to a hyperkinetic preconvulsive state which cannot be equated with hepatic coma. The primary mechanisms proposed for ammonia as a case of hepatic encephalopathy are a *direct* effect on neural membranes or on post-synaptic inhibition[31], and an *indirect* neuronal dysfunction.

There is no urea cycle in the brain, and ammonia removal involves a different pathway. In astrocytes, glutamine synthetase converts glutamate plus ammonia to glutamine. With excess ammonia, glutamate (an important excitatory neurotransmitter) is depleted, and glutamine accumulates. 1H (proton) MRS studies in hepatic encephalopathy show changes consistent with an increase in cerebral glutamine[32,33] The overall contribution of ammonia to the development of hepatic encephalopathy is difficult to quantify, particularly since there are also changes in other neurotransmitter systems.

Methionine derivatives, mainly mercaptans, induce hepatic encephalopathy. This has led to the view that certain toxins, particularly ammonia, mercaptans, fatty acids and phenols, act synergistically. These observations need evaluation with the better techniques now available.

Manganese

Blood and brain concentrations of manganese are increased in chronic liver failure. Manganese deposition is the most likely explanation for the hyper-intensity on MRI of the globus pallidus. Exposure of astrocytes to manganese produces Alzheimer type 2 changes as seen in hepatic encephalopathy.

False neurotransmitters

It has been proposed that dopamine and catecholamine mediated cerebral neurotransmission is inhibited by amines generated either by bacterial action in the colon or by the altered cerebral metabolism. The original hypothesis suggested that decarboxylation of some amino acids in the colon leads to the formation of b-phenylethanolamine, tyramine and octopamine so-called false neurotransmitters. These might replace the true transmitter.

An alternative approach to interference with normal neurotransmission is based on a change in the availability of precursors.. An increase in phenylalanine level in the brain leads to inhibition of dopa

production and the formation of false neurotransmitters such as phenylethanolamine and octopamine.

A change in this neurotransmitter system in hepatic encephalopathy has some support, since there is improvement after L-dopa and bromocriptine treatment. Serum and urinary octopamine levels are increased in hepatic encephalopathy.

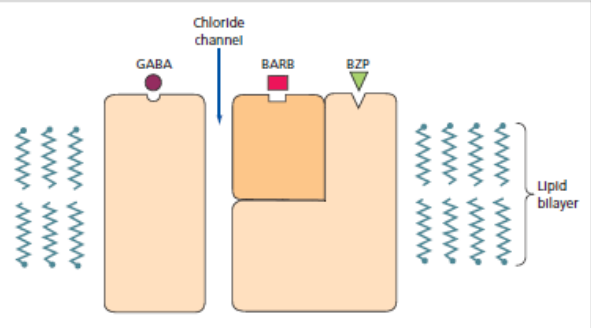
Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is involved in the control of cortical arousal and thus the conscious state and the sleep/wake cycle. It is also increased in the CSF and brain of patients with hepatic coma. In hepatic encephalopathy there are also other changes in serotonin metabolism including related enzymes (monoamine oxidase, MAO), receptors and metabolites (5-hydroxyindole acetic acid, 5-HIAA).

g-Aminobutyric acid (GABA) and endogenous benzodiazepines

GABAis the principal inhibitory neurotransmitter in the brain. It is usually synthesized from glutamate by glutamate dehydrogenase in presynaptic nerves and stored in vesicles. It binds to a specific GABA receptor in the postsynaptic membrane causing neuro-inhibition.

GABA is synthesized by gut bacteria, and that entering the portal vein is metabolized by the liver. There are increased GABA levels in the plasma of patients with liver disease and hepatic encephalopathy.



Simplified model of the GABAreceptor/ ionophore complex embedded in a postsynaptic neural membrane. Binding of any of the depicted ligands, gaminobutyric acid (GABA), barbiturates (BARB) or benzodiazepines (BZP), to its specific binding site increases chloride ion conductance through the membrane with resultant hyperpolarization and neuroinhibition

However, the focus on the GABA–benzodiazepine receptor suggest that endogenous benzodiazepines are present in patients with hepatic encephalopathy and that these may interact with the receptor complex and cause neuroinhibition. Stool from cirrhotic patients contains five times the benzodiazepine-like activity as stool from controls[34].

Both central benzodiazepine receptors (coupled GABA-A receptors) and peripheral type benzodiazepine receptors are increased in the brain in chronic liver failure. Flumezanil, a benzodiazepine antagonist is hence useful for treatment.[37]

Other metabolic abnormalities

Neuronal nitric oxide synthase may be increased in hepatic encephalopathy and make a contribution to the altered cerebral perfusion in chronic liver disease.

These patients are often *alkalotic.* This may result from toxic stimulation of the respiratory centre by ammonium, from administration of alkalis such as citrate in transfusions or with potassium supplements, or from *hypokalaemia*. Urea synthesis also consumes bicarbonate.

Hypoxia increases cerebral sensitivity to ammonia *Hypocapnia* follows and this reduces cerebral blood flow. The increase in the blood organic acids (lactate and pyruvate) is correlated with the reduction in CO2 tension.

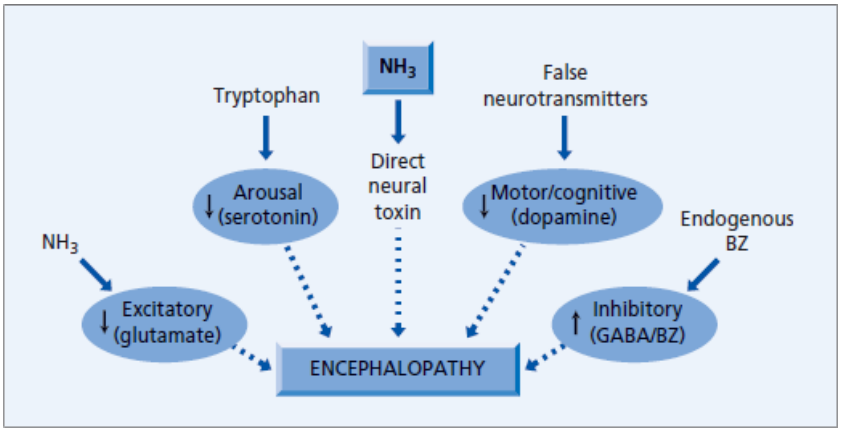
Changes in carbohydrate metabolism

Hypoglycaemic episodes are rare in chronic liver disease but may complicate fulminant hepatitis.

a-Ketoglutaric and pyruvic acids are transported from the periphery to the metabolic pool in the liver, and blood levels increase as the neurological state deteriorates. These levels probably reflect severe liver damage. The fall in blood ketones also reflects severity of hepatic dysfunction.

Astrocyte swelling

Studies using MR spectroscopy show ‘osmolytes’. It has been suggested that an associated increase in astrocyte hydration may be a major pathogenetic event in the development of hepatic encephalopathy



Multifactorial mechanism of hepatic encephalopathy. The altered neurotransmitter state leaves the brain more sensitive to other insults including narcotics, sepsis, hypoxia and hypotension. BZ, benzodiazepines; GABA, g-aminobutyric acid.

Conclusions

No single mechanism explains hepatic encephalopathy. The brain controls neuropsychiatric behavior through multiple inhibitory and stimulatory receptor mediated pathways. Although neurotransmitters are produced locally they depend upon substrates and influences from further afield. When the liver fails or there is portal-systemic shunting there is a complex pattern of changes which influence multiple neurotransmitter systems.

The effects of ammonia appear central to hepatic encephalopathy. Changes in glutamate, serotonin and endogenous benzodiazepine-mediated neurotransmission awaiting further study. The place of false neurotransmitters and GABA appears controversial.

Cerebral metabolism is undoubtedly abnormal in liver disease. This is thought to be an effect rather than the cause of neurotransmitter-mediated changes. In the chronic case, actual structural changes in the brain can be demonstrated. The end result is a brain with abnormal neurotransmitter function, which is unduly sensitive to insults, (opiates, electrolyte imbalance, sepsis, hypotension, hypoxia) that would be without effect in the normal patient.

Treatment of hepatic encephalopathy

Treatment is broadly divided into three areas.

1 Identification and treatment of the precipitating cause.

2 Intervention to reduce the production and absorption of gut-derived ammonia and other toxins.

3 Prescription of agents to modify neurotransmitter balance directly (bromocriptine, flumazemil), or indirectly (branched-chain amino acids). These are of limited clinical value at present.

The choice of treatment depends on the clinical picture: subclinical, acute or persistent chronic encephalopathy.

Table

Acute

Identify precipitating factor

Empty bowels of nitrogen-containing materials

stop haemorrhage

phosphate enema

Protein-restricted diet; raise dietary protein slowly with recovery

Lactulose or lactilol

Neomycin 1g four times a day by mouth for 1 week

Maintain calorie, fluid and electrolyte balance

Stop diuretics, check serum electrolyte levels

Chronic

Avoid nitrogen-containing drugs

Protein, largely vegetarian intake, at limit of tolerance

Ensure at least two free bowel movements daily

Lactulose or lactilol

Diet

In the acute attack dietary protein is reduced to 20g/day. Calorie intake is maintained at 2000cal/day or above, orally or intravenously. During recovery, protein is added in 10g increments on alternate days. Any relapse is treated by a return to the previous level.

It is important in cirrhotic patients to avoid protein restriction for a period any longer than is necessary since these patients have a higher than normal protein requirement (1.2 g/kg/day) to maintain in positive balance.

If animal protein is not well tolerated, vegetable protein may be used. The latter is less ammoniagenic and contains small amounts of methionine and aromatic amino acids.

Antibiotics

Neomycin, given orally, is very effective in decreasing gastrointestinal ammonium formation. Little Neomycin is minimally absorbed from the gut although blood levels have been detected and impaired hearing or deafness may follow its long-term use. Neomycin should be used with particular caution in patients with renal insufficiency. In acute hepatic coma, lactulose is given, and neomycin added if the response is slow since the two drugs seem to act synergistically[38].

Metronidazole (200mg four times per day orally) seems to be as effective as neomycin. Rifaximin, a non-absorbed derivative of rifamycin, is effective for grade 1–3 hepatic encephalopathy at a dose of 1200mg/day.

Lactulose and lactilol

The human intestinal mucosa does not have an enzyme to split these synthetic disaccharides. When given by mouth *lactulose* reaches the caecum where it is broken down by bacteria predominantly to lactic acid. The osmotic volume of the colon is increased. The faecal pH drops. The growth of lactose-fermenting organisms is favoured and organisms such as bacteroides, which are ammonia formers, are suppressed.

The colonic fermentative bacteria prefer lactulose to blood when both are present. It may ‘detoxify’ short-chain fatty acids produced in the

presence of blood and proteins. Faecal acidity would reduce the ionization and hence absorption of ammonia; however faecal ammonia is not increased. Lactulose more than doubles the colonic output of bacterial mass and 'soluble' nitrogen which is then no longer available for absorption as ammonia.

The aim of treatment with lactulose is to produce acid stools without diarrhoea. The dose is 10–30ml three times a day and is adjusted to produce two semi-soft stools daily. This improves level of consciousness[44].

Lactilol (b-galactoside sorbitol) is a second-generation disaccharide easily produced in chemically pure crystalline form, which can be dispensed as a powder. It is not broken down or absorbed in the small intestine, but is metabolized by colonic bacteria. Lactilol seemed to be as effective as lactulose in chronic and acute portal-systemic encephalopathy.[39]

Lactulose or lactose enemas may be used and are superior to water[41]. All enemas must be neutral or acid to reduce ammonium absorption. Magnesium sulphate enemas can cause dangerous hypermagnesaemia. Phosphate enemas are safe.

Sodium benzoate and L-ornithine -L-aspartate

Sodium benzoate promotes urinary excretion of ammonia and is as effective as lactulose and is less expensive. L-ornithine-L-aspartate treatment promotes hepatic removal of ammonia by stimulating residual hepatic urea cycle activity and promoting glutamine synthesis, particularly in skeletal muscle[42] and helps in improving level of consciousness.

Levodopa and bromocriptine

If portal-systemic encephalopathy is related to a defect in dopaminergic neurotransmission then replenishment of cerebral dopamines should be beneficial. Dopamine does not pass the blood–brain barrier, but its precursor, levodopa, does and can cause temporary arousal in acute hepatic encephalopathy[43].

Flumazenil

This is a benzodiazepine-receptor antagonist which can induce transient, variable but distinct improvement in some patients with hepatic encephalopathy associated with fulminant liver failure or cirrhosis[37]. Overall results showed improvement in neurological score in 15% of treated patientcompared with 3% on placebo. EEG improved in 25% of treated patients compared with 4% on placebo.

Branched-chain amino acids

In cirrhotic patients the serum branched chain amino acids valine, leucine and isoleucine are low, and aromatic amino acid levels are increased. The reduced ratio of branched-chain to aromatic amino acids has been related to the development of hepatic encephalopathy through increased supply of precursors of neurotransmitters.

Infusions of solutions containing a high concentration of branched-chain amino acids have been used to treat acute and chronic hepatic encephalopathy with conflicting results.

Other precipitating factors

Patients are extremely sensitive to sedatives and whenever possible these are avoided. If an overdose is suspected, the appropriate antagonist should be given. If the patient is uncontrollable and some sedation is necessary, a small dose of temazepam or oxazepam is given; morphine and paraldehyde are absolutely contraindicated.

Drugs known to induce hepatic coma such as oral amino acids and diuretics are disallowed. Potassium deficiency can be treated by fruit juices or by effervescent or slow-release potassium chloride.

Temporary hepatic support

Complicated methods of temporary hepatic support are not applicable to hepatic coma in the cirrhotic. Such a patient is either terminal or can be expected to come out of coma without them.

Hepatic transplantation

This may be the ultimate answer to the problem of chronic hepatic encephalopathy. One patient with a history of 3 years showed marked improvement lasting 9 months following transplantation. Another patient with chronic hepato-cerebral degeneration and spastic paraparesis showed remarkable improvement after orthotopic liver transplantation.

MINIMAL HEPATIC ENCEPHALOPATHY

MHE is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects together with a normal neurological examination.

The pathogenesis of MHE is not yet clear. Subcortical alterations in the basal ganglia has been suggested as a possible anatomical site responsible for the subclinical changes of this entity.[8]The selective reduction in glucose consumption in the area of the cyngulate gyrus, a nucleus involved in the attention process, coupled with focal alterations of cerebral perfusion support this hypothesis.[9]

The relation of subclinical changes to protein metabolism and plasma amino acid imbalance, the reduction in cerebral blood flow and the improved response of neuropsychological tests after therapeutic manipulations (which are applied in clinically overt HE), suggest the impact of the liver disease on brain function.[7] The incidence of MHE is estimated to vary from 30% to 84% in apparently healthy, non-encephalopthic cirrhotic patients, depending on the diagnostic criteria used.[10]

The Cerebral Blood Flow range in healthy young subjects (age, 23-42 years) was 44-61 m1/100 g/min; in patients with grade I + II encephalopathy (mean ± SEM) it was 32.8 23.6 m1/100 g/min in acute (age, 28 ± 8 years) and 37.0 ×.3.3 m1/100 g/ min in chronic liver patients (age, 51 ± 2 years). In grade III ± IV encephalopathy it was 28.7 ± 3.8 m1/100 g/min in acute (age, 28 ± 3 years) and 32.9 ± 3.7 m1/100 g/min in chronic patients (age, 49 ± 3 years). A marked reduction of the CBF was seen in hepatic encephalopathy, irrespective of the etiology of the disease.[10]

Fifty percent of the patients had an abnormal Number Connection Test according to the standard recommended procedure, in contrast only 7% of the patients had an abnormal NCT when scores corrected for age were used.

Combining the results of the spectral EEG and the psychometric tests corrected for age yielded a higher prevalence of SHE (23%) than when each test method was used alone (17% vs. 10% abnormal, respectively). Severity of liver disease correlated with the presence of SHE, because the prevalence of abnormal tests increased from 14% in Child-Pugh grade A to 45% in Child-Pugh grade B or C. Age above 40 years and an elevated blood ammonia level were significant determinants related to an abnormal EEG. Using a combination of spectral EEG and two psychometric tests with age-corrected normal values a low prevalence of SHE in patients with Child A liver cirrhosis was found. Older patients with an elevated arterial ammonia are more prone to develop SHE than younger patients with an equal arterial ammonia concentration.[12].[13]

Although the diagnosis of symptomatic HE is a diagnosis of exclusion, based mainly on a careful global and neuropsychiatric examination, MHE is not a clinically evident entity and thus, for their detection, requires specific neuropsychological and neurophysiological examination.[14]

The interest in identifying MHE has made researchers to formulate and use 60 tests and eight batteries in various studies. These can be divided into four major groups.[15]

I. Psychometric or Neuropsychological tests

II. Electrophysiological or Neurophysiological tests

III. Neuroimaging testing

IV. Tests of cerebral metabolism

I. PSYCHOMETRIC OR NEUROPSYCHOLOGICAL TESTS

Based on the hypothesis that mental changes can precede overt neurological symptoms of HE., Zeegen et al in the early 1970.s, first demonstrated an abnormal score in approximately one third of 39 apparently healthy cirrhotic patients previously operated for portal decompression, using the Reitan trail making tests.

The statement of the Consensus Conference of the 11th World Congress of Gastroenterology proposed that at least two of the following psychometric examinations should be used: NCT-A, NCT-B, BlDes, DST. A standardized test battery that includes the NCT-A and -B, the line-tracing test, the serial-dotting test and the DST is recommended[6].

The newly developed computerized psychometric tests, Posner test, Ternberg Paradigm appear to be very promising tools, but experience is still limited.

2. ELECTROPHYSIOLOGICAL OR NEUROPHYSIOLOGICAL TESTS

Although EEG is the most widely used neurophysiological diagnostic tool for the detection of clinically apparent HE, its diagnostic role in MHE is minor. With a percentage of abnormal examinations ranging between 8%-35% among cirrhotics without overt HE, it is considered less sensitive than psychometric tests[7]

Apart from EEG, several investigators have used evoked potentials (EP) such as the P300 (P300 eventrelated potentials), the SSEP (somatosensory-evoked potentials), the BAEP (brain stem auditory-evoked potentials) and the VEP (visual-evoked potentials) can be used[21.]

The P300 examination is an endogenous EP that is regarded as representing stimulus evaluation processes. In contrast to the conventional EPs, the response on P300 does not depend on the physical properties of the stimulus, but rather on the meaning of the stimulus to the patient. In this test, the response to two different stimuli, visual and acoustic, is measured and the patient is asked to identifity a predefined stimulus. A prolongation of the P300 latency to acoustic stimuli is observed in patients with MHE.

3. NEUROIMAGING TESTS

Brain imaging provides no useful information for the assessment of MHE. Computer tomography must be used only for differential diagnosis.

Although cranial magnetic resonance imaging shows characteristic abnormalities in cirrhotic patients (symmetric pallidal hyperintensities in T1-weighted images), these changes do not correlate with the grade of encephalopathy. Proton magnetic resonance spectroscopy and positron emission tomography (PET) are two relatively new imaging methods and the experience in diagnosis of MHE with these is very limited.[9]

4. TEST OF CEREBRAL METABOLISM

There is a very little data about tests of cerebral metabolism in diagnosis of MHE.

CLINICAL SIGNIFICANCE OF M.H.E.

Impact on daily life:

The significance of MHE diagnosis is still a subject of debate. Several investigators have reported a negative influence on daily functioning. Other studies suggest a possible relation between MHE and the subsequent development of episodes of overt HE.

The reduction in the ability of these patients to carry out activities (driving a car, performing at work) probably reflects the

neuropsychological deficits founded in MHE. It has been reported that a percentage of between 44% and 70% of cirrhotics with the diagnosis of MHE show an impairment in their ability to drive an automobile. On the other hand, other investigations, did not revealed differences in quality of automobile driving between cirrhotics with MHE and healthy subjects.[48]

Quality of life:

Patients with MHE experience a poor quality of life with serious difficulties in sleep, hobbies, recreation and deterioration of body care. The performance of SIP (Sickness Impact Profile) questionnaires showed highest scores of disability on the areas of social interaction, alertness, emotional behavior, mobility, sleep/rest, home management and recreation and pastimes. Sleep abnormalities are frequent in all cirrhotics and may be related to alterations of circardian function, or could reflect anxiety and depression as a result of living with chronic disease.

Although named “minimal”, minimal hepatic encephalopathy (MHE) can have a far-reaching impact on quality of life, ability to function in daily life and progression to overt hepatic encephalopathy. Importantly, MHE has a profound negative impact on the ability to drive a car and may be a significant factor behind motor vehicle accidents. A crucial aspect of the clinical care of MHE patients is their driving history, which is often ignored in routine care and can add a vital dimension to the

overall disease assessment. Driving history should be an integral part of care in patients with MHE.

The prognostic value of MHE:

The clinical repercussions of detecting MHE are still unknown. A possible prognostic value of psychometric alterations in the subsequent development of overt HE and survival is suggested by several authors, but very few studies can confirm these statements. Most of these have been limited to patients with advanced liver disease (portal systemic shunts, decompensated cirrhosis), and the follow up time was very short: less than 12 months. Only two long term follow up studies have confirmed that MHE is an independent risk factor for the development of HE. The predictive value of MHE on survival is also a subject of debate and the relationship between severity of liver disease and psychometric alterations is not yet clarified.

The Number Connection Test

- Assesses the ability of the patient to connect a series of numbers from 1 to 25
- Evaluates the cognitive and psychometric functions
- Graded according to the time taken for the completion of the test and the time taken for correction of errors.
- Grading

0 - 15 – 30 sec

1 - 31 – 50 sec

2 - 51 – 80 sec

3 - 80 – 120sec

4 - > 120 sec

Arterial Ammonia

Arterial estimation more useful and correlates better with encephalopathy than venous levels.

Normal values range between 9 – 33 micromoles/litre

Electroencephalographic Analysis

EEG shows Generalised slow electrical activity

High amplitude low frequency waves and triphasic waves are significant.

Other Assessment:

Evoked potential show abnormality in 90% patients.

Positron Emission Tomography and Magnetic Resonance Spectroscopy are more specific for diagnosis.

MATERIALS AND METHODS

4. MATERIALS AND METHODS

The study was conducted in the Coimbatore Medical College Hospital, Coimbatore. The cases were selected from the general medical wards, the intensive care unit and the Medical Gastroenterology out patient department.

50 cases of compensated cirrhosis were chosen over a time span of 6 months. 50 healthy controls were chosen from the volunteers. Only patients with Ultra-sound proven cirrhosis were chosen to be included in the study. Patients with signs of liver decompensation like jaundice, history of previous admissions for hepatic encephalopathy, massive Gastro-intestinal bleed were excluded from the study. Patients who developed features of hepatic encephalopathy were excluded from the study.

Patients with other co-morbidity like severe congestive cardiac failure or renal failure or severe respiratory failure were also excluded.

42 males and 8 females were finally included as the study population.

A detailed history was recorded giving special emphasis to rule out any subtle performance impairment. Detailed history was also taken to

probe into the etiology of cirrhosis.A detailed clinical examination was done to rule out any signs of decompensation. Minimal ascites was not taken as an exclusion criteria.

Minimal evidence of portal hypertension was not taken as exclusion criteria.

All the baseline investigations were done and a CNS examination carried out to rule out other causes of encephalopathy. Patients above 75 years of age were excluded as the incidence of dementing illness was high in the age group.

A number connection test was given to the patient and the control simultaneously. After proper explanation of the procedure test was administered. Before interpreting the results it was made sure that they understood the procedure properly. The time taken to complete the test was added to the time taken to correct errors added.

An arterial blood sample was obtained from radial artery and was sent for ammonia analysis and an electroencephalogram was performed in all study subjects and in 10 healthy controls.

The studies, especially the number connection test were repeated just before discharge of the patients after treatment.

RESULTS AND ANALYSIS

RESULTS AND ANALYSIS

NUMBER CONNECTION TEST:

- All controls completed the NCT correctly within 60 (Normal) seconds
- Any time greater than 60 seconds was taken as significant and an indication of MHC
- 36% of cases were found positive (time more than 60 seconds) by the test

The grading system commonly followed is as follows

GRADE	NCT completion time in seconds	Remarks
0	15 to 30	No MHE
1	31 to 50	High normal
2	51 to 80	Suggests MHE
3	81 to 119	Highly suggests MHE
4	>120	

Table.1

The prevalence of MHE in compensated cirrhosis by the number connection test is given in the following tables

PREVALANCE OF MHC IN CIRRRHOTICS BY NCT

NCT POSTIVE	NUMBER	PERCENTAGE
Males	15	30%
Females	2	4%
Total	17	36%

Table.2

SERUM AMMONIA

- Arterial blood for estimation of Ammonia analysis was done
- 15 patients whose blood was drawn for Arterial Blood Gas analysis (ABG) was taken as controls. None were having liver cirrhosis or hepatic encephalopathy
- The normal ammonia level standardized for the laboratory was 10 to 30 micro mol/litre
- Any value above 30 micro mol/l was taken as positive
- 50% cases were found to have positive ammonia levels (> 33 mciromols) none in controls.

PREVALANCE OF MHC BASED ON AMMONIA ANALYSIS

ARTERIAL AMMONIA > 30 µmol/L	**NUMBER**	**PERCENTAGE**
Male	18	36%
Female	6	12%
Total	25	48%

Table.3

ELECTROENCEPHALOGRAPHY (EEG)

- All 50 patients and 10 controls were taken up for EEG analysis
- None of them were on sedatives or any cerebroactive drugs and none were epileptic
- All other causes for encephalopathy were ruled out by clinical examination and baseline investigation

EEG was taken as significant if any of the following were present:

1. Diffuse slowing of waves
2. High amplitude, low frequency waves
3. Triphasic waves

- 4 of the patients had significant findings (8%)
- None of the controls had any of these findings

PREVALENCE OF MHE BASED ON EEG ANALYSIS

EEG CHANGES POSITIVE	NUMBER	PERCENTAGE
Male	3	6%
Females	0	0%
Total	3	3%

Table.4

PREVALENCE OF MHE IN CIRRHOSIS USING A COMBINATION OF TESTS

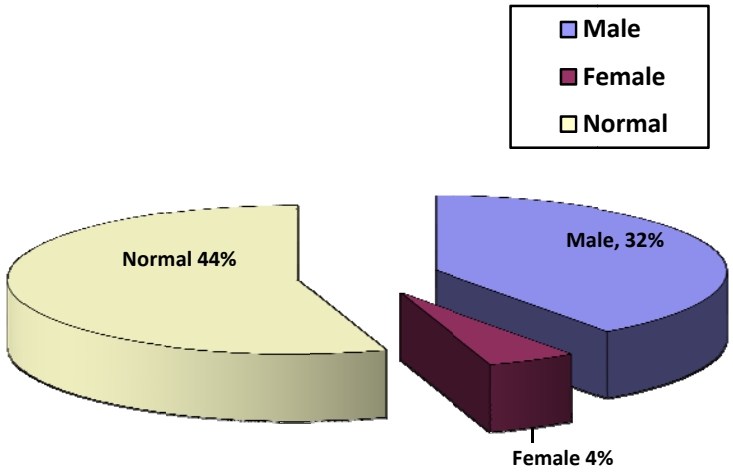
NAME OF TESTS	NUMBER POSITIVE	PERCENTAGE
Number connection Test + EEG	Males : 3 Females : 0 Total : 3	Males : 6% Females : 0% Total : 6%
Number connection test + Arterial Ammonia	Males : 15 Females : 1 Total : 7	Males : 30% Females : 2% Total : 32%
EEG + Arterial Ammonia	Males : 2 Females : 0 Total : 2	Males : 4% Females : 0% Total : 4%
NCT + Arterial Ammonia + EEG	Male : 2 Females : 0 Total : 2	Males : 4% Females : 0% Total : 4%

Table.5

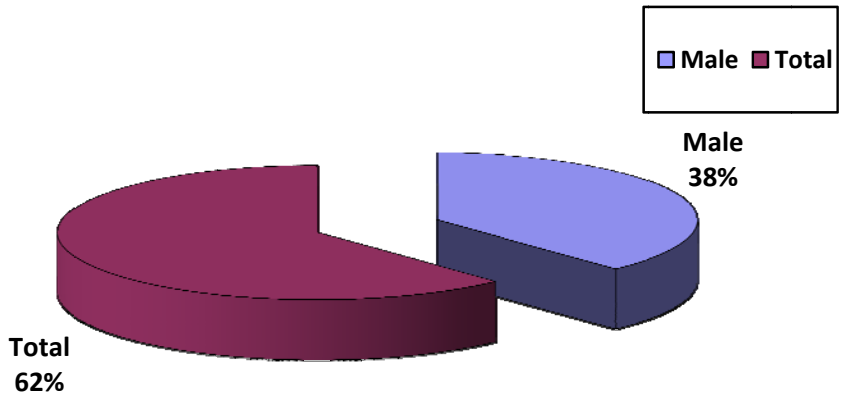
OBSERVATION

PREVALENCE OF MHE IN MALES WITH CIRRHOSIS

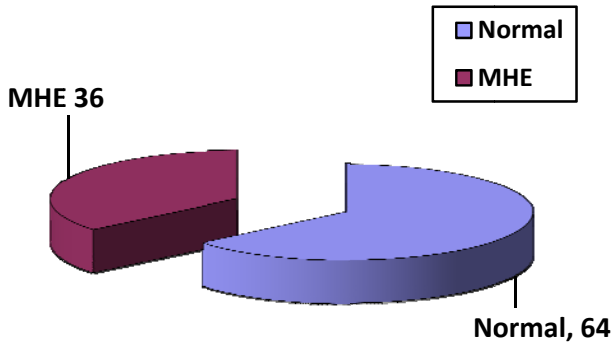
By NCT



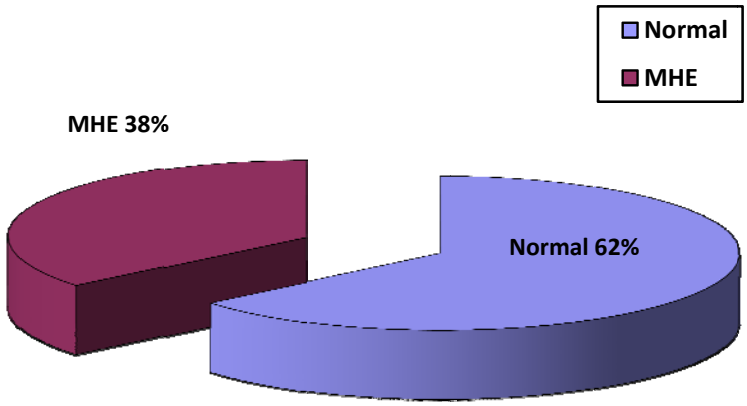
PREVALENCE OF MHE IN MALES WITH CIRRHOSIS



PREVALENCE OF MHE IN FEMALES WITH CIRRHOSIS



PREVALENCE OF MHE IN PATIENTS WITH CIRRHOSIS



DISCUSSION

6.DISCUSSION

- In this study 50 cases of compensated cirrhotics were evaluated for presence of Minimal Hepatic Encephalopathy.

- In this study we defined minimal hepatic encephalopathy based on psychometric analysis,[13] by way of the Number Connection Test, since earlier studies have proved that the abnormal psychometric test as one of the earliest manifestation of minimal hepatic encephalopathy. Based on the NCT this study found a prevalence of 38% MHE amongst the compensated cirrhotics studied

- Minimal hepatic encephalopathy was defined in our study based on the prolonged time taken to complete the NCT and/or Electroencephalography changes/ or a combination of electroencephalography and serum ammonia rise/ or a combination of serum ammonia and number connection test.

- High serum ammonia alone was not taken as indicative of minimal hepatic encephalopathy as it was found by many studies not to correlate with the presence of Minimal hepatic encephalopathy.

- The total percentage of cases diagnosed as having minimal hepatic encephalopathy in our study using the above criteria was 38%

- Out of the 19 patients tested positive for minimal hepatic encephalopathy 16 were males and 3 were females

- In a study conducted by Quero et.al in Holland[13] about MHE in cirrhotics with NCT and EEG, showed a prevalence of 24%. Correlation was done using arterial ammonia and PET scan. Magnetic Resonance Spectroscopy was also used for correlation.

- In a German study[47] published in the Journal of Hepatology in 1998 July, pages 45 to 49 volume 28 No.1 the prevalence of MHE was estimated to be 45% by various psychometric tests including

the Number Connection Test thus establishing it as a simple bedside tool for assessment of the presence of MHE in the cirrhotics

- In a study conducted by Amodio et al in Italy[46] it was found that using the NCT and Line tract test the prevalence of Minimal Hepatic encephalopathy was estimated to be 28% but estimates by spectral EEG was only 10%

- In comparison, our study shows a prevalence of minimal hepatic encephalopathy in the group by number connection test to be 34% and that by electroencephalogram to be 6%.

CONCLUSION

7. CONCLUSIONS

- The prevalence of Minimal Hepatic Encephalopathy in compensated cirrhotics in our study is 38%.

- There is no significant difference in the prevalence rate between males and females. (38% Vs 37%)

- Number Connection Test and other psychometric tests are useful as bedside tools in estimating Minimal Hepatic Encephalopathy.

- Psychometric test positivity does not correlate well with Electro-encephalographic changes in the diagnosis of Minimal Hepatic Encephalopathy.

- Evaluating a cirrhotic patient for MHE is essential for its impact on day to day functionality like driving, operating machineries and social interaction apart from other activities like driving.