Dissertation on

"PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR THE DETECTION OF MINIMAL HEPATIC ENCEPHALOPATHY IN SOUTH INDIAN PATIENTS WITH LIVER CIRRHOSIS"

Submitted in partial fulfillment for the Degree of

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CERTIFICATE

This is to certify that the dissertation entitled **"PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR THE DETECTION OF MINIMAL HEPATIC ENCEPHALOPATHY IN SOUTH INDIAN PATIENTS WITH LIVER CIRRHOSIS"** is a bonafide original work done by **Dr. G. KUMARAVEL**, in partial fulfillment of the requirements for M.D. GENERAL MEDICINE BRANCH – I examination of the Tamilnadu Dr. M.G.R Medical University to be held in April 2015, under my guidance and supervision in 2014

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I hereby solemnly declare that the dissertation entitled **"PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR THE DETECTION OF MINIMAL HEPATIC ENCEPHALOPATHY IN SOUTH INDIAN PATIENTS WITH LIVER CIRRHOSIS"** is done by me at Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai during 2014 under the guidance and supervision of **Prof. K.S. CHENTHIL M.D.,** This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai towards the partial fulfillment of requirement for the award of M.D. Degree in General Medicine (Branch I)

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CONTENTS

ABBREVIATIONS:

HE	-	Hepatic encephalopathy
MHE	-	Minimal hepatic encephalopathy
PHES	-	Psychometric hepatic encephalopathy score
NCT-A	-	Number connection test A
NCT-B	-	Number connection test B
DST	-	Digit symbol test
LDT	-	Line drawing test
CDT	-	Circle dot test
HRQoF	-	Health related quality of life
LFT	-	Liver function test
CT	-	Computed tomography
MRI	-	Magnetic resonance imaging
EEG	-	Electroencephalogram

ABSTRACT

BACKGROUND:

Hepatic encephalopathy is the commonest complication of cirrhosis. In patients with cirrhosis a spectrum of neuro psychiatric abnormalities exist ranging from indiscriminable changes in cognition(MHE) to clinically obvious changers in intellect, behavior, motor functions and consciousness(overt HE)

AIM:

To detect minimal hepatic encephalopathy in cirrhotic patients in south indian population using PHES.

METHODS:

In this study 40 cases and 40 controls were taken. Cases are cirrhotic patients without obvious neurological findings.

PHES score includes NCTA,NCTB, DST,LDT,CDT.

RESULTS:

Out of the 40 patients 19 cases(47.5% are found to have MHE

CONCLUSION:

PHES is statistically significant in detecting MHE in cirrhotic patients.

KEYWORDS:

Hepatic encephalopathy

Minimal hepatic encephalopathy

Psychometric hepaticencephalopathy score

INTRODUCTION

Hepatic encephalopathy is the commonest complication of cirrhosis.in patients with cirrhosis,a spectrum of neuropsychiatric abnormalities exist ranging from clinically indiscernible changes in cognition(MHE) to clinically obvious changes in intellect, behavior, motor function and consciousness.(overt HE) .most common precipitating factors for HE are sepsis, gastrointestinal hemorrhage, constipation, dehydration, uremia, hypokalemia, alkalosis.

MHE is used to describe patients with cirrhosis who are clinically normal but who show abnormalities of cognition and neurophysiological variables.

MHE – detrimental effect on HRQOL.

-ability to perform complex tasks such as driving.

-increases the risk of developing overt HE.

-early identification – improves HRQOL and prognosis.

Inflammation and raised serum ammonia levels is the main pathogenic factors for HE.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

- To standardize the PHES in healthy south Indian population and evaluate the prevalence of MHE among south Indian patients with liver cirrhosis

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Weight of normal adult liver is 1400 to 1600 grams. Approximately 2.5% of body weight. Cirrhosis is the twelfth leading cause of death in US, and its burden is increasing worldwide. The term cirrhosis is derived from Greek medicine meaning orange yellow color of diseased liver. Cirrhosis is caused by many etiologies like alcoholic , viral hepatitis, metabolic, drugs, cardiac causes, etc.

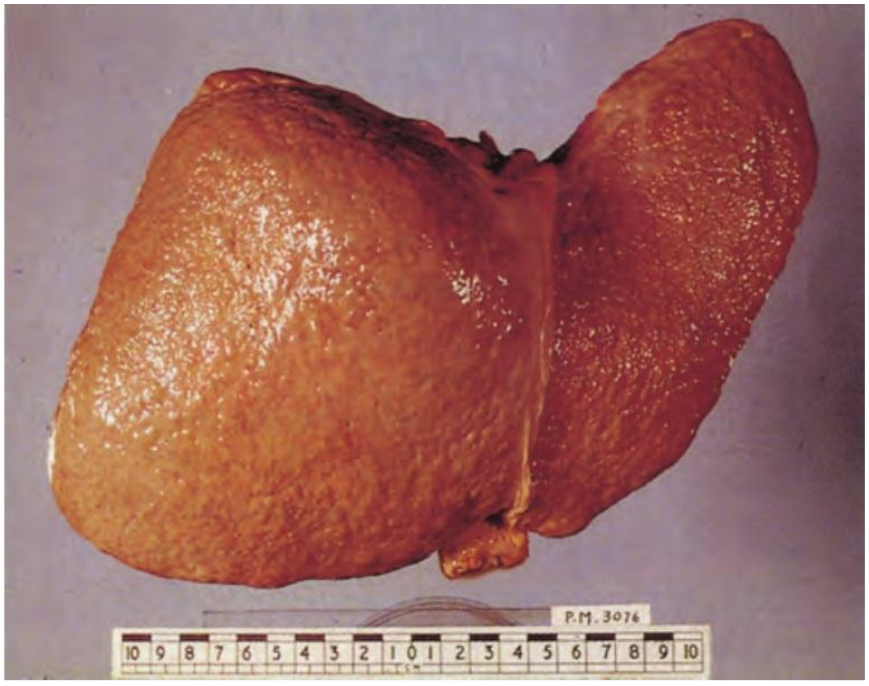
Cirrhosis is defined by three morphologic features.

1- Bridging fibrous septa- linking portal tract with one another and portal tract with terminal hepatic veins.

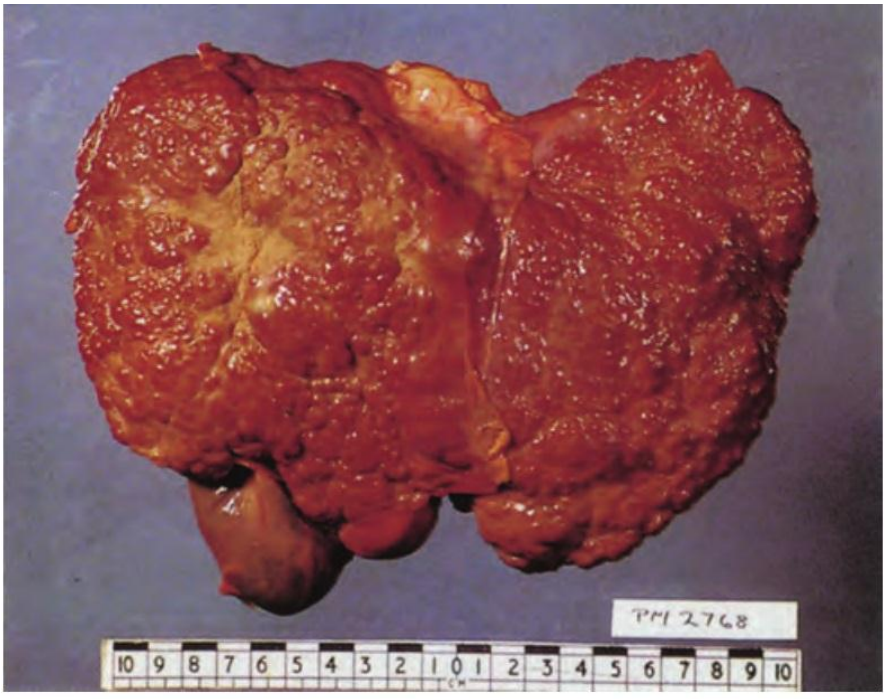
2-parenchymal nodules-hepatocyte encircled by fibrosis.

3-disruption of liver architecture.

Up to forty percentage of patients with cirrhosis were asymptomatic until the occurrence of decompensation in the form of bleeding varices, spontaneous bacterial peritonitis and hepatic encephalopathy, previously cirrhosis and fibrosis was thought to be irreversible but new evidence says that fibrosis may be reversible in some alcoholics after abstaining and in some chronic hepatitis b and hemochromatosis patients.



The small finely nodular liver of micronodular cirrhosis.



The grossly distorted coarsely nodular liver of macronodular cirrhosis.

PATHOGENESIS

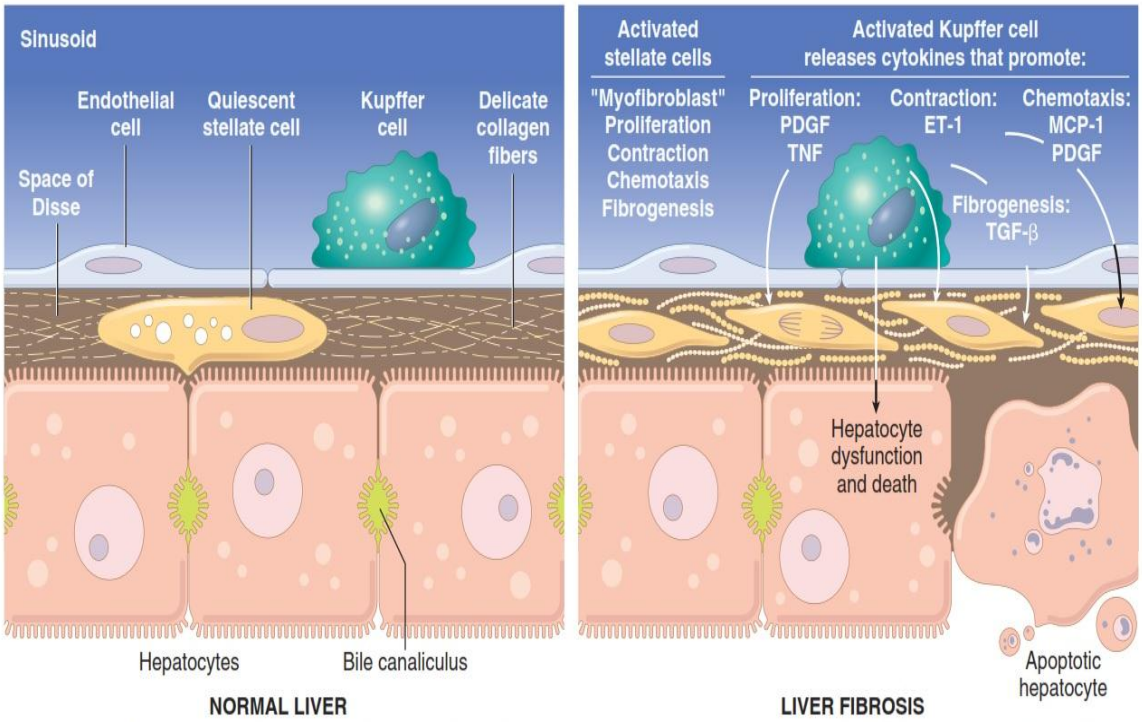
The main pathogenic process in cirrhosis is

1- Death of hepatocyte

2- Extracellular matrix deposition

3-vascular regeneration.

Proliferation of hepatic cells and their activation into highly fibrogenic cells is the main mechanism of fibrosis.



Stellate cell activation and liver fibrosis. Kupffer cell activation leads to secretion of multiple cytokines. Platelet-derived growth factor (PDGF) and tumor necrosis factor (TNF) activate stellate cells, and contraction of the activated stellate cells is stimulated by endothelin-1 (ET-1). Fibrogenesis is stimulated by transforming growth factor β (TGF-β). Chemotaxis of activated stellate cells to areas of injury is promoted by PDGF and monocyte chemotactic protein-1 (MCP-1).

RISK FACTORS:

Heavy alcohol consumption

Health care professionals

Obesity

Tattooing

Unprotected sex

Toxic and chemical exposures

Certain medications

IV drug abusers sharing intravenous needles

ETIOLOGY:

Alcoholic liver disease

Viral:

- Chronic hepatitis C
- Chronic hepatitis B
- Cytomegalovirus
- Epstein Barr virus

Metabolic:

- NAFLD/NASH
- Hemochromatosis
- Wilson’s disease
- Diabetes mellitus
- Alpha 1 anti-trypsin deficiency
- Cystic fibrosis
- Tyrosinosis
- Hereditary fructose intolerance
- Glycogen storage diseases

Drug induced:

- Amiodarone
- Methotrexate
- Nitrofurantoin

Biliary cirrhosis

Primary biliary cirrhosis

Primary sclerosing cholangitis

Autoimmune cholangiopathy

Cardiac:

Chronic right heart failure

Tricuspid regurgitation

Cryptogenic

CLINICAL FEATURES:

Patient with chronic liver disease may be identified in the following ways [3]:

1. Patients may be identified on routine clinical examination.
2. They might have undergone laboratory/radiological imaging or some procedures which incidentally found out the presence of chronic liver disease.
3. They may present in a decompensated state.
4. Some patients may never come to clinical attention.[4]

HISTORY:

This should include questions to identify risk factors for chronic liver disease like history of alcohol intake, hepatitis, jaundice, diabetes, illicit drug use, blood transfusion, any surgery, family history of liver diseases and autoimmune conditions.

Questioning should also include those related to symptoms of chronic liver disease like fatigue, pedal edema, weight loss, confusion, bleeding tendency.

Symptoms may vary from asymptomatic to overt features of decompensation. Patients with chronic liver disease due to hepatitis C may have muscle wasting, large ascites and overt hepatic encephalopathy but only mild jaundice while patients with chronic liver disease due to primary biliary cirrhosis may have deep icterus but no muscle wasting. Patients may experience fatigue, anorexia, weight loss. Cutaneous manifestations may include jaundice, spider naevi, paper money skin, palmar erythema, white nails, disappearance of lunulae, and finger clubbing.

Increased conversion of androgens to estrogen occurs in adipose tissue, skeletal muscle which may be responsible for loss of axillary and pubic hair, gynecomastia, and impotence. Anemia may be due to folate

deficiency, hemolysis, and hypersplenism. Thrombocytopenia is usually the first marker of hypersplenism. Coagulopathy results from decreased production of coagulation factors and diminished absorption of vitamin

SYMPTOMS:

Fatigue, weakness

Poor appetite

Muscle wasting

Jaundice

Breast enlargement in men

Ascites

Parotid gland enlargement

Altered sleep pattern, somnolence,

Pruritus

Blood vomiting

Redness of palms

Impotence, loss of libido

SIGNS

Signs may be classified as those associated with etiology and those associated with decompensation.

SIGNS ASSOCIATED WITH ETIOLOGY:

Alcohol related:

Parotid enlargement

Dupuytren's contracture

Peripheral neuropathy

Cerebellar signs

Testicular atrophy

Wilson's disease:

Kayer Fleischer ring

Hepatomegaly

Dystonia, tremors, involuntary movements

Hemochromatosis:

Increased pigmentation

Hepatomegaly

NASH:

Xanthomas, xanthelesma

Corneal arcus

Viral hepatitis:

Tattoo marks, injection marks

Right heart failure:

Peripheral edema

Elevated JVP

SIGNS OF DECOMPENSATION:

Icterus

Ascites

Peripheral edema

Ecchymosis

Asterixis

Encephalopathy

Bleeding varices

Spider angiomata

Cruveilheir Baumgarten murmur

Fetor hepaticus

Caput medusae

COMPLICATIONS:

Portal hypertension

Ascites

Hypersplenism

Variceal bleeding

Hepatorenal syndrome

Porto pulmonary hypertension

Hepatic encephalopathy

Hepatopulmonary syndrome

Malignant transformation.

DIAGNOSIS:

Many times the presence of chronic liver disease is suggested by laboratory investigations. Common laboratory investigations performed under the label LFT (liver function tests) are

1) Enzyme tests

    Serum aminotransferases (AST, ALT)

    Serum alkaline phosphatase

    Gamma Glutamyl Trans peptidase

2) Serum bilirubin

3) Assess synthetic function

    Serum albumin

    Prothrombin time and INR

Aminotransferases:

Both aspartate transaminase and alanine transaminase may be elevated but usually <3 times the upper normal limit, but can be normal in advanced stages of liver disease. Chronic liver disease other than alcohol will have AST/ALT ratio less than one.

Alkaline phosphatase:

Elevated in most forms of chronic liver disease but will be less than three times the upper normal limit. High levels are noted in

1) Primary biliary cirrhosis
2) Primary sclerosing cholangitis

Gamma Glutamyl Trans peptidase:

It is considered moderately specific for alcoholic liver disease because of two reasons

1) Alcohol induces hepatic microsomal GGT synthesis.
2) Alcohol causes leakage of GGT from hepatocytes.

Serum bilirubin:

It may be normal in compensated state but elevated bilirubin indicates fairly advanced liver disease.

In primary biliary cirrhosis elevated bilirubin indicates poor prognosis.

Serum albumin:

As liver function deteriorates albumin levels also decreases as it is solely synthesized in liver but hypoalbuminaemia is not specific for chronic liver disease as it may be decreased in other conditions like

1) Nephrotic syndrome

2) Protein losing enteropathy

3) Malnutrition

Prothrombin time:

Increases as liver disease progresses since coagulation factors are produced in liver.

Serum globulin:

Elevated levels of globulin are seen in cirrhosis as various antigens are shunted away from liver, reach systemic circulation and elicit immunological response. Increased levels of IgM are seen in primary biliary cirrhosis, increased IgA is seen in alcoholic liver disease.

Serum sodium:

Hyponatremia in chronic liver disease patients indicates poor prognosis, and is due to high levels of ADH seen in cirrhotic patients.

Hematological investigations:

Anemia:

May be due to blood loss

Folate deficiency

Direct toxicity of alcohol

Hemolysis

Anemia of chronic disease

Hypersplenism

Thrombocytopenia:

Due to hypersplenism, but the platelet count doesn't drop below 50000 cells/ mm^3. May cause bleeding if associated with coagulopathy.

Leucopenia, neutropenia:

Due to hypersplenism and splenic margination.

INVESTIGATIONS TO DETERMINE THE ETIOLOGY OF CHRONIC LIVER DISEASE:

Alcoholic liver disease:

History of alcohol abuse

AST: ALT ratio > 2 due alcohol induced deficiency of pyridoxal phosphate

Liver biopsy may show features typical of alcoholic hepatitis, Mallory's hyaline, liver cell necrosis.

Chronic hepatitis C:

Anti HCV antibody

HCV RNA quantification

Liver biopsy to establish the severity of liver disease.

Chronic hepatitis B:

HBsAg

HBeAg

HBV DNA Quantification

NASH:

associated features of metabolic syndrome like hyperglycemia, hyperlipidemia.

Liver biopsy

Primary biliary cirrhosis:

Elevated alkaline phosphatase

Anti-mitochondrial antibody is considered to be the hallmark of primary biliary cirrhosis

ERCP

Primary sclerosing cholangitis:

Associated with inflammatory bowel disease.

Contrast cholangiography shows diffuse, focal strictures and dilatation of bile ducts giving it a beaded appearance.

Anti-smooth muscle antibody (ASMA)

Anti-nuclear antibodies

Anti-neutrophilic cytoplasmic antibody(ANCA)

Autoimmune hepatitis:

Increased gamma globulin levels

Anti-LKM1 antibody

Anti-ALC antibody

Hemochromatosis:

Family history of cirrhosis

Increased skin pigmentation

Fasting transferrin saturation

More than 60% in men

More than 50 % in women

Plasma ferritin

>300mg/dl in men

>200mg/dl in women

Genetic testing

Liver biopsy

Wilson's disease:

Kayer Fleisher rings on slit lamp examination.

Decreased serum ceruloplasmin.

24 hour urinary copper >100mg

Copper content >200mg/g of liver tissue in liver biopsy.

Haplotype analysis.

Alpha 1 anti-trypsin deficiency:

Decreased serum alpha1 anti-trypsin levels.

Genetic testing

Right sided heart failure:

Electrocardiogram, Echocardiogram

RADIOLOGICAL IMAGING

Ultrasound abdomen:

Provide useful information regarding liver size, echo texture.

Useful screening to identify development of HCC (hepatocellular carcinoma) in a patient with preexisting cirrhosis.

Doppler ultrasound:

Provides information regarding blood flow in portal vein, hepatic veins.

Assess size of portal vein, splenic vein.

Identify presence of collaterals.

Computed tomography Abdomen:

To assess liver size, shape.

To identify liver nodule.

To detect HCC.

MRI Abdomen:

Most useful in evaluating the biliary tree

To detect malignancy.

Transient elastography (Fibro scan):

Noninvasive method to assess the stiffness and evaluate liver fibrosis and cirrhosis.

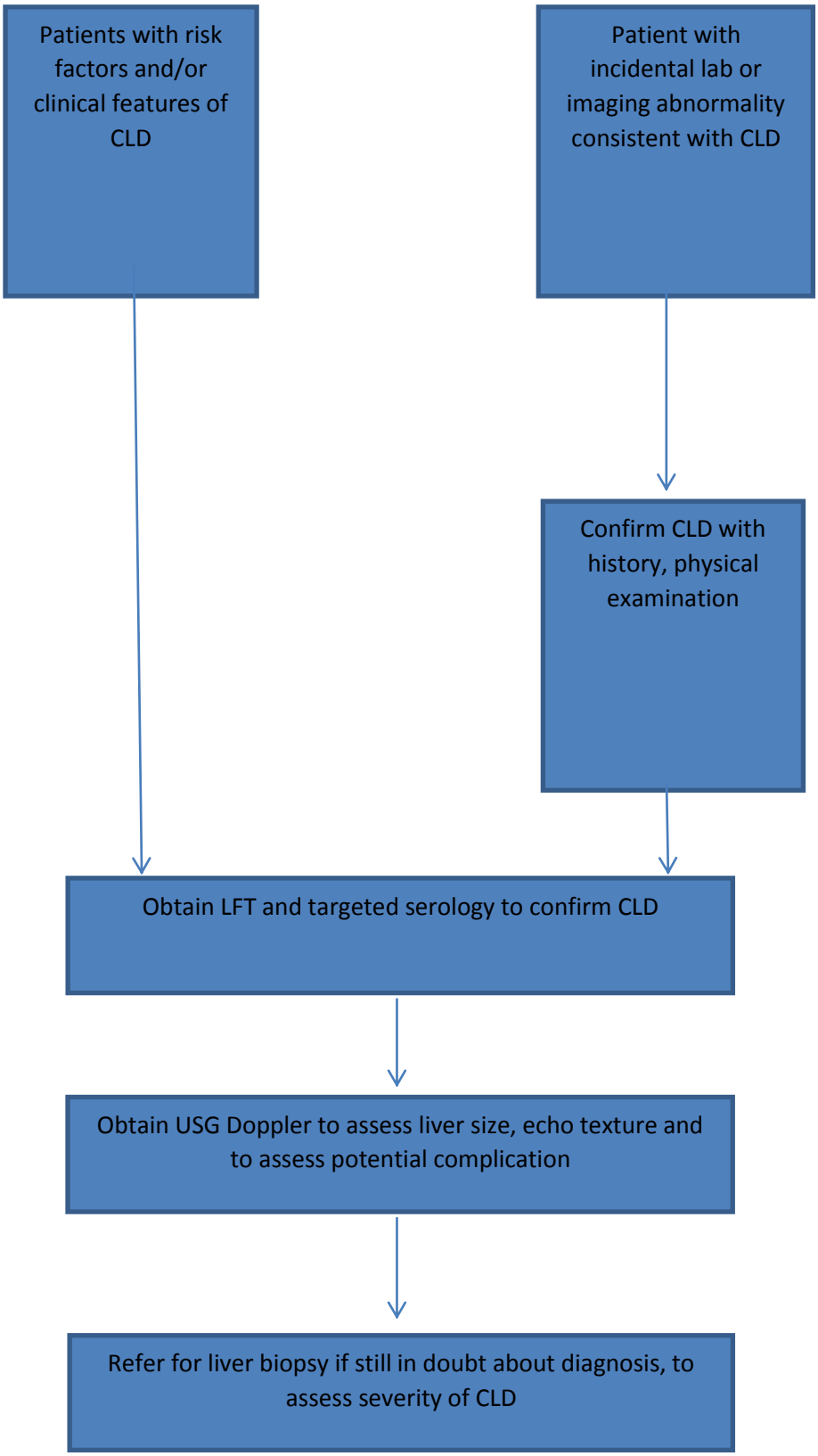
Liver biopsy:

The gold standard test to aid in identifying the etiology of chronic liver disease.

To grade the disease activity.

To assess the severity of chronic liver disease.

DIAGNOSTIC ALGORITHM: CHRONIC LIVER DISEASE



ASSESSMENT OF SEVERITY AND PROGNOSIS

Severity may be assessed by

1) Child Pugh's scoring system
2) MELD scoring system
3) Liver biopsy

CHILD PUGH'S SCORING SYSTEM:

Clinical and Lab Criteria.	Points		
	1	2	3
Ascites	None	Slight (diuretic responsive)	Moderate (diuretic unresponsive)
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dl)	<2	2-3	>3
Encephalopathy	None	Grade 1 and 2	Grade 3 and 4
Prothrombin time INR	<1.7	1.7-2.3	>2.3

Class A: 5-6 survival at one and two year 100% and 65%, Class B: 7-9 survival at one and two year 80% and 60%, Class C: 10-15 survival 45% and 35%.

MELD SCORING SYSTEM:

MELD (model for end stage liver disease) was initially developed to assess short term prognosis in patients with chronic liver disease who undergo TIPS[2,5] (Trans jugular intra-hepatic Porto systemic shunt) but its usefulness to assess the prognosis and severity of chronic liver disease has been well validated.It consists of three variables

1) Serum bilirubin
2) Serum creatinine
3) Prothrombin time INR(International Normalized Ratio)

SCORE	THREE MONTH MORTALITY (%)
>40	71.3
30-39	52.6
20-29	19.6
10-19	6
<9	5

MANAGEMENT OF CHRONIC LIVER DISEASE

GENERAL MANAGEMENT :

As the patient once lands in cirrhosis, liver will never regain its normal structure, but symptomatic measures can go a long way in improving the quality of life. Liver has such a regenerative capacity that even though structurally abnormal its functional capacity may be achieved.

MANAGEMENT IN A COMPENSATED STATE:

Adequate diet [6]:

30-40 Kcal/kg body weight

1.2-1.5g of protein per kg of body weight

Abstinence from alcohol.

Weight loss if obese.

Early detection and treatment of complications.

Treatment of specific cause:

Antiviral therapy for chronic hepatitis B and C

Steroids and immunosuppressant for autoimmune hepatitis.

Ursodeoxycholic acid in early stages of primary biliary cirrhosis.

Chelation therapy for Wilson's disease.

Venesection for hemochromatosis.

DECOMPENSATED STATE:

Treatment is aimed at

Identification of precipitating factors

Early detection and management of complications.

Hepatic encephalopathy:

Avoidance of precipitating factors.

Lactulose 40-120 ml daily

Lactitol 20-40g daily

Rifaximin 400mg three times a day.

Liver transplantation.

Portal hypertension:

Propranolol 40-80 mg two times a day.

Ascites and peripheral edema:

Sodium restriction <2 g per day.

Fluid restriction if there is Hyponatremia.

Spironolactone starting dose 100 mg , maximum dose 400mg per day

Furosemide 40 mg per day, maximum 160 mg per day

Large volume paracentesis with intravenous salt poor albumin

Hepatorenal syndrome:

Avoidance of nephrotoxins

Intravenous albumin

Midodrine

Octreotide

Spontaneous bacterial peritonitis

Cefotaxime 2 g IV tds

Norfloxacin 400 mg twice daily

EMERGING ANTIFIBROTIC STRATEGIES:

The ever increasing understanding of mechanisms leading to fibro genesis has led to development of anti fibrotic therapy a reality in near future. The potential approach includes

Decrease and or modify host response to stellate cell activation

Down regulate stellate cell activation.

Stimulate programmed cell death of stellate cell.

Increase the degradation of scar matrix.

ROLE OF LIVER TRANSPLANTATION:

Liver transplantation is considered when liver no longer has its ability to do its various functions. The following are the most common indication for liver transplantation

Hepatitis C, B

Alcoholic liver disease

Autoimmune liver disease

Primary biliary cirrhosis

MINIMAL HEPATIC ENCEPHALOPATHY

- Minimal hepatic encephalopathy is the mild form of spectrum of hepatic encephalopathy. It is defined as the mild neurocognitive and psychomotor disorder present in patients with cirrhosis. These mild neurocognitive disorder primarily affects attention. Speed of processing information coordination motor abilities that are not recognizable on standard neurological examination.

- Zeegan et al was the first to describe this condition in 1970 when they discovered that 38% Of patients scored abnormal in reitan trailmaking test [number connection test] who had undergone portal decompression surgery.

- Terminologies: previously they used the following terminologies for describing patients with MHE.

    1. Early HE,
    2. low-grade HE
    3. latent HE
    4. subclinical HE

EPIDEMIOLOGY:

Majority of cirrhotic patients develop MHE.But there are no accurate data on the incidence of MHE.

- Overt HE occurs in 30 – 50% of cirrhotic patients and in 10 – 50 % of patients with TIPS.
- Prevalence of MHE has been reported to vary between 30% -84% in cirrhotic patients. Reasons for large variation include presence of prior overt HE, age, severity of liver disease, alcohol etiology, TIPS, surgical Porto-systemic shunts, presence of esophageal varices.

PATHOGENESIS:

The main pathogenic mechanism is increased ammonia level and an inflammatory response leads to swelling of astrocytes in brain, leading to fluid accumulation in brain and cerebral edema.

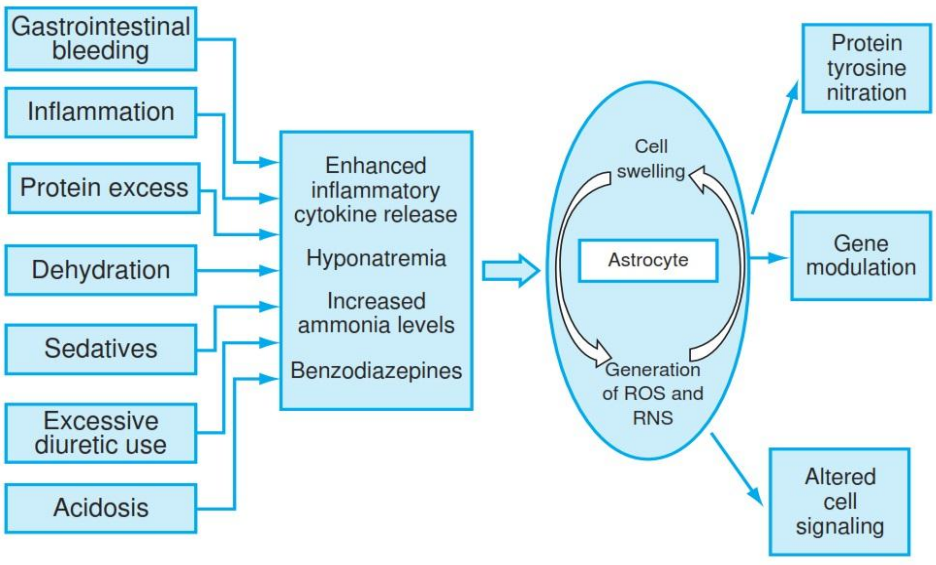
AMMONIA:

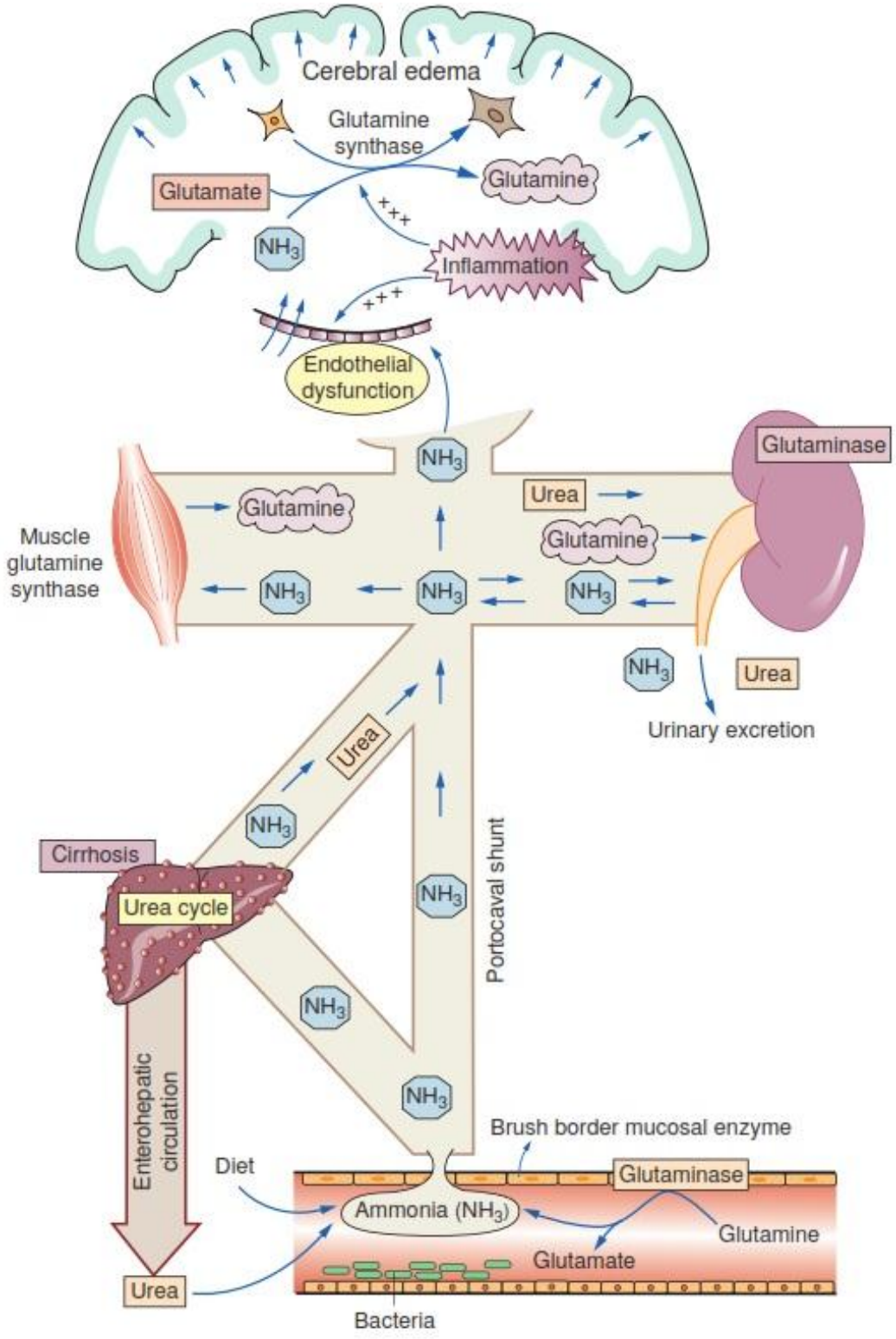
- Protein metabolism produces ammonia. Normally ammonia reaches liver where it is detoxified in urea cycle and urea is produced. Urea is excreted through the kidneys.

- In cirrhotic patients ammonia is not metabolized in liver, so it reaches the brain. Astrocytes are the only cells in brain that can metabolize ammonia.in brain ammonia combines with glutamate in the presence of glutamine synthetase to produce glutamine. GLUTAMINE IS AN OSMOLYTE. So water moves in astrocyte and swelling occurs leading on to cerebral edema and increased intracranial tension.

- In experimental studies it was found that administration of methionine sulfoxemine [glutamine synthetase inhibitor] prevents astrocyte swelling.

- Astrocyte swelling is compensated by release of osmolyte myoinositol and taurine from inside the cell. Over time the cells change in form and become “ALZHEIMER TYPE II” astrocytes.




Cerebral edema
Glutamine synthase
Glutamate
Glutamine
NH3
Inflammation
Endothelial dysfunction
Glutaminase
Urea
Glutamine
Muscle glutamine synthase
Urinary excretion
Portocaval shunt
Cirrhosis
Urea cycle
Enterohepatic circulation
Brush border mucosal enzyme
Diet
Ammonia (NH3)
Bacteria

INFLAMMATION:

Sepsis is a common precipitating factor for decompensation of liver disease in previously stable patients.Serum levels of inflammatory markers

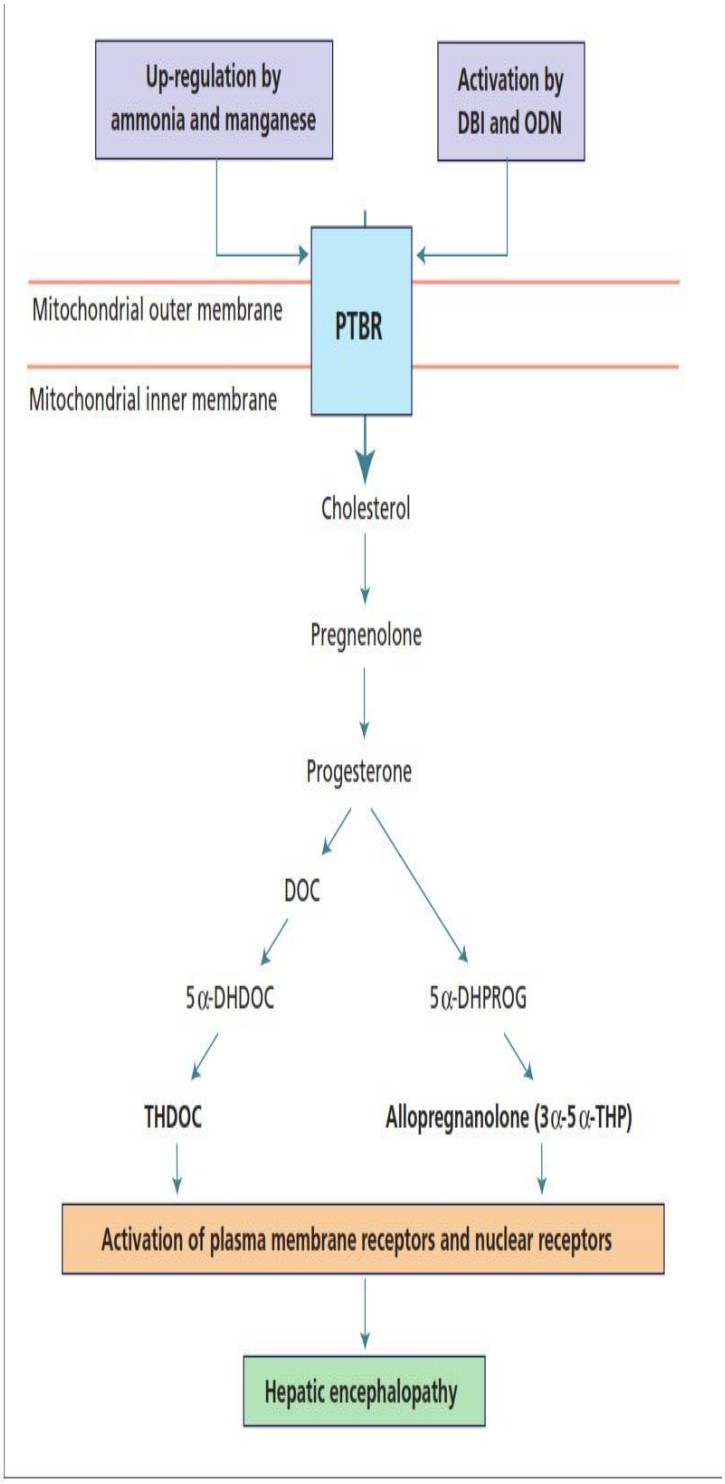
- C-RP,
- WBC count,
- IL-6

Were very much increased in patients with MHE, then in patients without MHE.

- Once SIRS is treated these markers came to normal level and patients also did better in psychometric tests. TNF, IL-6 increases diffusion of ammonia into astrocytes.

NEUROSTEROIDS:

- 18 kDa translocator protein is unregulated in microglial cells that are activated by inflammation. Increased expression of this receptor results in increased mitochondrial synthesis of neurosteroids.
- Ammonia, manganese which accumulate in patients with liver failure act on these receptors and increases neurosteroid production.
- Neurosteroids act on GABA-A receptor and enhances GABA nergic tone.



The role of the peripheral benzodiazepine receptor (PTBR) in the synthesis of neurosteroids. Uptake of cholesterol into the mitochondrion follows activation of the PTBR localized at the inner/ outer mitochondrial membrane. The isoquinoline binding protein subunit expression of the PTBR is up-regulated in the presence of ammonia and manganese. Following activation of PTBR by agonists such as diazepam binding inhibitor (DBI) or octadecaneuropeptide (ODN) cholesterol is converted by a series of stages to the neurosteroids 3α-5α-tetrahydroprogesterone (allopregnanolone) and 3α-5α-tetrahydrodesoxycorticosterone (THDOC). Brain accumulation of these neurosteroids leads to activation of both membrane and nuclear receptors which may subsequently alter neurotransmission and gene expression.

OXIDATIVE AND NITROSATIVE STRESS:

Astrocytes exposed to

- ammonia,
- inflammatory cytokines,
- benzodiazepines,
- hyponatremia

Produce more reactive nitrogen species [RNS] and reactive oxygen species [ROS].Acute swelling of astrocytes occurs as astrocytes are exposed to ROS, RNS. Intramitochondrial ammonia mediates release of ROS, RNS through calcium dependent pathways. ROS is also involved in nitration of tyrosine residues in intracellular proteins. Tyrosine nitration affects the permeability of blood brain barrier and promotes astrocyte swelling.

MANGANESE:

- Manganese is a neurotoxin that accumulate in basal ganglia of patients with cirrhosis with extensive Porto caval shunts.it has been detected by MRI brain. Manganese induces changes in astrocytes of basal ganglia and promotes formation of Alzheimer type II

astrocytes. Manganese deposition in basal ganglia might explain tremors [parkinsonian symptoms] in some patients with HE.

ZINC:

- Zinc is a substrate of urea cycle enzymes.in cirrhotic patient's zinc is depleted. Activity of ornithine transcarbamylase increases after zinc supplementation and this in turn lead to increased excretion of ammonia ions. However there is conflicting clinical data regarding supplementation of zinc in management of MHE.

SEROTONIN:

- Serotonin a neurotransmitter is important for regulation of sleep, locomotion and circadian rhythm. Serotonin metabolism is sensitive to hyperammonemia and Porto systemic shunting. This suggests a role for serotonin in early neuronal manifestation of HE.

BRANCHED CHAIN AMMINOACIDS [BCAA] AND FALSE NEUROTRANSMITTERS:

- In severe liver dysfunction there is imbalance between aromatic amino acids AAA [tyrosine, tryptophan and phenylalanine] and branched chain amioacids BCAA [leucine, isoleucine and valine]. In the CNS AAA and BCAA share a common transport.as a

consequence of increased AAA false neurotransmitters [phenylethanolamide and octopamide] are produced with subsequent development of HE.

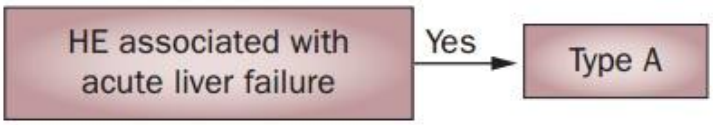
INTESTINAL FLORA:

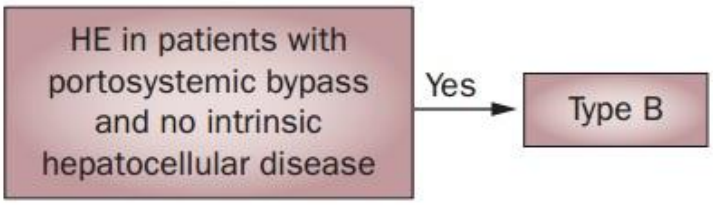
- Endotoxins and intestinal flora are an important link between ammonia, inflammation and MHE. In the study conducted by zaho et al, compared to healthy controls, in cirrhotic patients imbalance of intestinal flora has been demonstrated. They found a decrease in counts of bifidobacterium and an increase in counts of aerobes [enterobacter] and anaerobes [clostridium].in cirrhotic patients there has been a significant faecal overgrowth of pathogenic E.coli and staphylococcus species. Faecal growth of lactobacillus species increased after treatment with synbiotics.this was associated with reduction in blood ammonia and reversal of MHE in 50% of patients.

CLASSIFICATION OF HEPATIC ENCEPHALOPATHY:

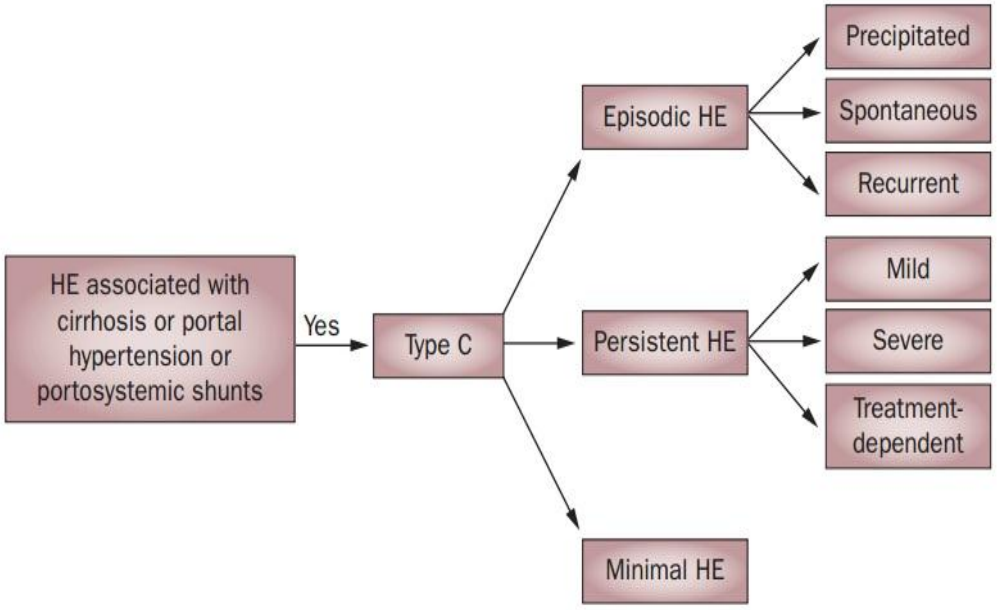
Hepatic encephalopathy is classified into 3 types by the working party at the 1998 world congress of gastroenterology, Vienna, Austria.

- TYPE A
- TYPE B





- TYPE C -Type c is again divided into 3 categories.



DIAGNOSIS:

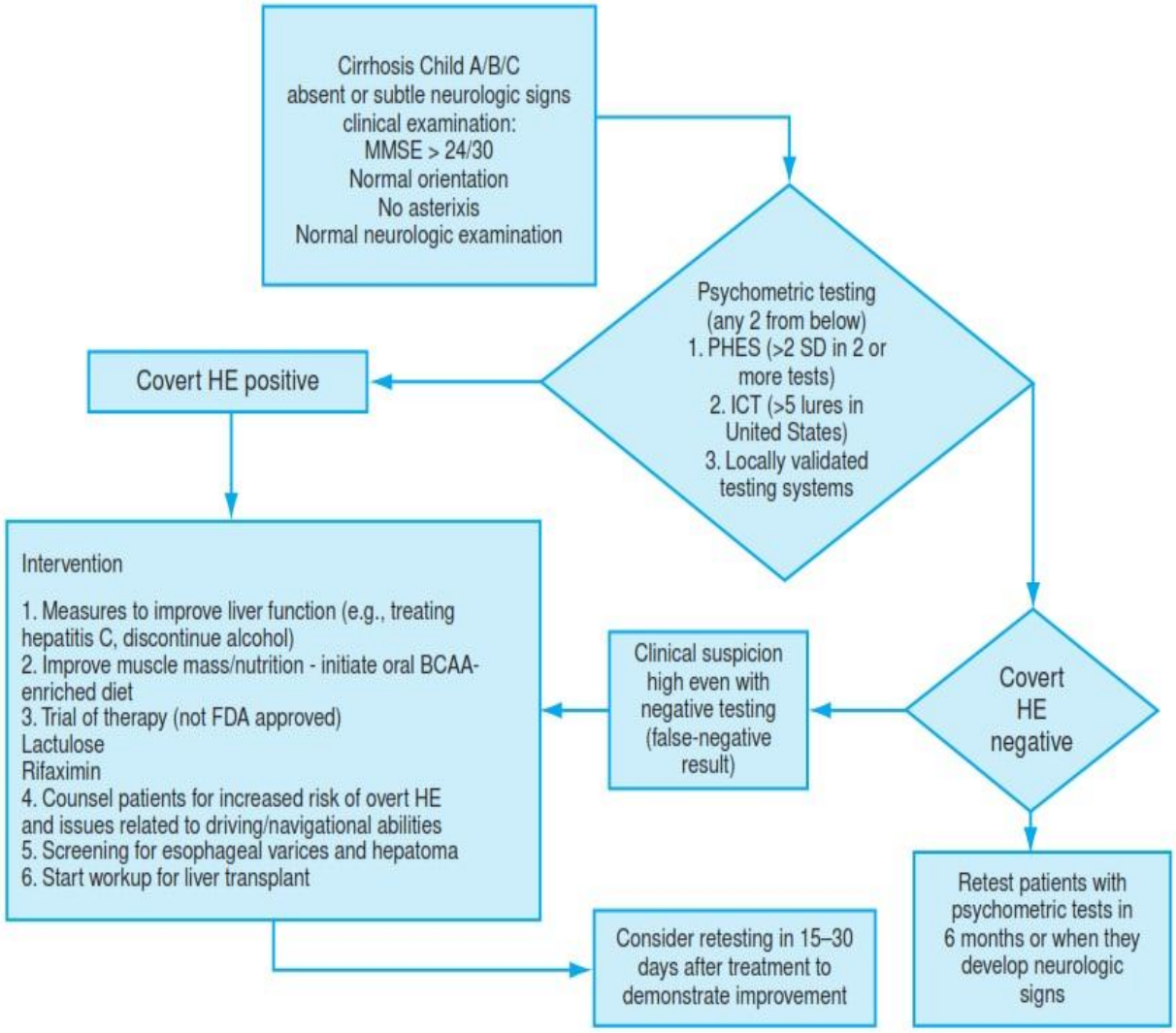
- Approach to hepatic encephalopathy comprises of

➢ 1.Exclusion of other causes of encephalopathy

➢ 2. Identification of precipitating cause

➢ 3. Trial of empiric treatment for HE.

This is called as triparitite strategy.



RULE OUT OTHER CAUSES OF ENCEPHALOPATHY:

- Hypoxia ,hypercapnia
- Acidosis, uremia
- Sensitivity to CNS drugs
- Electrolyte changes
- Prior seizure or stroke[post ictal confusion]
- Delirium tremens
- Wernicke –korsakoff syndrome
- Intracranial hemorrhage
- CNS sepsis
- Cerebral edema, intracranial hypertension
- Hypoglycemia
- Pancreatic encephalopathy
- Drug intoxication

IDENTIFICATION OF THE PRECIPITATING CAUSE OF HEPPATIC ENCEPHALOPATHY:

- Sepsis
- Gastrointestinal hemorrhage
- Constipation
- Dietary protein overload
- Uremia
- Hypokalemia
- Alkalosis
- Dehydration
- Poor compliance with lactulose therapy
- Prior anesthesia
- Prior portal decompression procedure
- Bowel obstruction or ileus
- Superimposed hepatic injury
- Development of hepatocellular carcinoma

INITIATING EMPPIRIC TREATMENT FOR HEPATIC ENCEPHALOPATHY:

- Lactulose ,oral dose of 15-30 ml twice daily
- Rifaximin ,oral dose of 550 mg twice daily
- Neomycin ,oral dose of 5oo mg four times daily
- Metronidazole, oral dose of 250 mg four times daily
- Lactulose bowel wash

A rapid response to this empiric treatment confirms diagnosis of HE, lack of response within 72 hours indicates consideration of further treatment options.

DIFFERENTIAL CAUSES:

Many conditions have similar symptoms to HE, exclusion of these conditions is important.

- If there is change in mental status, SDH should be excluded as cirrhotic patients have coagulopathies and increased risk of falls.
- Sepsis related organ failure, as cirrhotic patients are associated with an increased risk of sepsis.
- Medication induced adverse effects.

Many cirrhotic patients have atleast one or multiple coexisting precipitating factors capable of inducing an episode of HE.

DIAGNOSIS OF MINIMAL HEPATIC ENCEPHALOPATHY:

The diagnosis of MHE is based on

1. Confirmation of a disease that can cause MHE, such as cirrhosis or Porto systemic shunts.
2. Exclusion of normal mental status on clinical examination [absence of clinical evidence of hepatic encephalopathy.
3. Demonstration of abnormalities in cognition and neurophysiological variables
4. Exclusion of other neurological disorders

In cirrhotic patients a wide spectrum of neurological and neurophysiological abnormalities are present.it may extend from no HE, MHE to overt HE.

DIAGNOSTIC TESTS:

Various diagnostic tests are devised to detect MHE, they are

1. Serum ammonia
2. Clinical scales

   West Haven criteria
3. Neuropsychometric tests

   Paper and pencil tests

   Computerized tests
4. Electro physiologic tests

   EEG

   Spectral EEG

   P300 EVOKED potentials

   Critical flicker frequency
5. Brain imaging

   CT brain,

   MRI,

   Spectroscopy

SERUM AMMONIA:

Serum ammonia levels correlate well with severity of HE. Routinely it is not done as it would not change the approach to diagnosis or in management.it is difficult to do in clinics as it has to be transported within 20 minutes to laboratory with ice packing.

Differential Diagnosis of Hyperammonemia
Acute liver failure
Chronic kidney disease
Cigarette smoking
Cirrhosis
Gastrointestinal bleeding
Inborn errors of metabolism
Proline metabolism disorders
Urea cycle disorders (e.g., carbamyl phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, argininosuccinate lyase deficiency, *N*-acetyl glutamate synthetase deficiency)
Medications
Alcohol
Diuretics (e.g., acetazolamide)
Narcotics
Valproic acid
Muscle exertion and ischemia
Portosystemic shunts
Technique and conditions of blood sampling
High body temperature
High-protein diet
Tourniquet use

CLINICAL SCALES:

A number of scales has been discovered to diagnose HE. The first clinical scale was discovered by parson-smith and his colleagues in 1957.

WEST HAVEN CRITERIA:

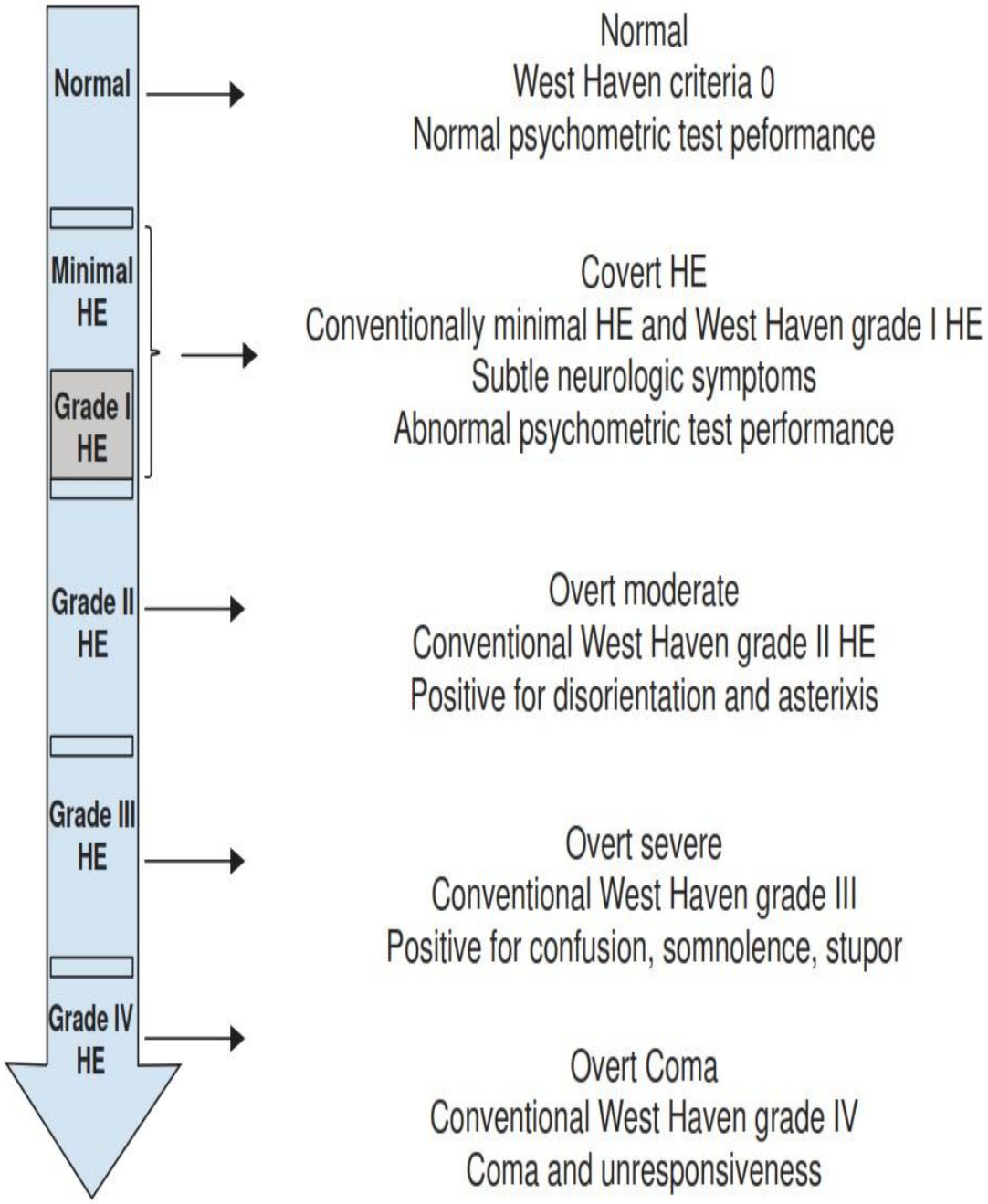
This criteria is used in a number of studies. This criteria was developed in 1977 by CONN et al. this criteria semi quantitatively grades a patients mental state by subjective assessment of intellectual function, behavior, alteration of consciousness and neuromuscular function.

ORIGINAL VERSION:

- Comprises of 4 grades however this scale showed substantial variability between observers in assessing low grades of HE.

MODIFIED VERSION:

- Amodio and colleagues in 2004, proposed a modification to the above criteria that introduced objective scales for assessing individual components of the criteria.


Normal
Minimal HE
Grade I HE
Grade II HE
Grade III HE
Grade IV HE
Normal
West Haven criteria 0
Normal psychometric test peformance
Covert HE
Conventionally minimal HE and West Haven grade I HE
Subtle neurologic symptoms
Abnormal psychometric test performance
Overt moderate
Conventional West Haven grade II HE
Positive for disorientation and asterixis
Overt severe
Conventional West Haven grade III
Positive for confusion, somnolence, stupor
Overt Coma
Conventional West Haven grade IV
Coma and unresponsiveness

CHESS:

- Reliability of West Haven criteria can be improved by using along with the clinical hepatic encephalopathy staging scale [CHESS].It contains 9 items.
- Minimal score = 0,maximal score = 9.this scale scores HE from 0 [normal mental state] to 9 [deep coma]table 3.

Hepatic encephalopathy scoring algorithm [HESA]:

- This was first devised by Hassanein et al.it was first used in multicenter study. This algorithm assess the utility of extracorporeal albumin dialysis in management of patients with HE. This is particularly useful in assessing patients with low grades of HE.

NEUROPSYCOMETRIC TESTS:

It consists of

1. Pencil and paper tests

2. Computerized tests. The tests should be objective, reliable, sensitive and valid.

PENCIL AND PAPER TESTS:

These tests are employed to assess impairments in domains such as attention, processing speed, visuospatial functioning and response inhibition.

PHES:

Psychometric hepatic encephalopathy scoring system .this scoring is based on the results of hamster who used a battery of more than 20 psychometric tests to patients with cirrhosis and controls. This test was designed to identify subtle cognitive changes that are characteristic of MHE in cirrhotic patients. Normal data for comparison was obtained from Germany, Italy, and Spain.

Abnormal results strongly correlated with changes in brain imaging. This test was declared as the "GOLD STANDARD " for diagnosis of MHE in cirrhotic patients by the working party of the 1998 world congress of Gastroenterology, Vienna, Austria. Due to lack of US specific normative data, this test failed to gain popularity in USA. This scoring comprises of

- 1.number connection test A
- 2.number connection test B

- 3.digit symbol test
- 4.line drawing test
- 5.circle dotting test

Impairment of more than 2SD in two or more tests is necessary for diagnosis of MHE.

RBANS:

Repeatable battery for the assessment of neurological status.

This was initially used to diagnose neurocognitive disorders such as dementia, stroke, multiple sclerosis, traumatic brain injury and bipolar disorders in USA.it is effective n screening MHE.it is a paper and pencil test and takes 20-25 min to administer.

- It measures working memory, visuospatial function [figure copy and line orientation], verbal and cognitive processing speed.

COMPUTERISED PSYCOMETRIC TESTS:

- In the last seven years a number of computerized tests have been developed. These tests are potential in assessing patients with HE.

INHIBITORY CONTROL TEST:

This is the most popular currently available computerized test.

This test asses 2 different cognitive domains

- 1.attention
- 2.response inhibition,

Principle – based on

1. Targets
2. Lures.

A series of different alphabet sequences are flashed on a computer screen and patient is asked to respond when x is followed by y or vice versa-so called target. And asked not to respond when x is followed by x or y followed by y.-so called lure.

A lure response more than 5 out of 40 attempts detects MHE.This test shows close correlations with other scores and might be approved for diagnosis of MHE.

CDR Computerized assessment system:

This cognitive drug research system was devised to detect neurocognitive changes in cirrhotic patients. This test contains seven tests and measures continuity of attention, power of attention, quality of continuous memory, quality of episodic memory and speed of memory. This test shows good correlation with PHES.

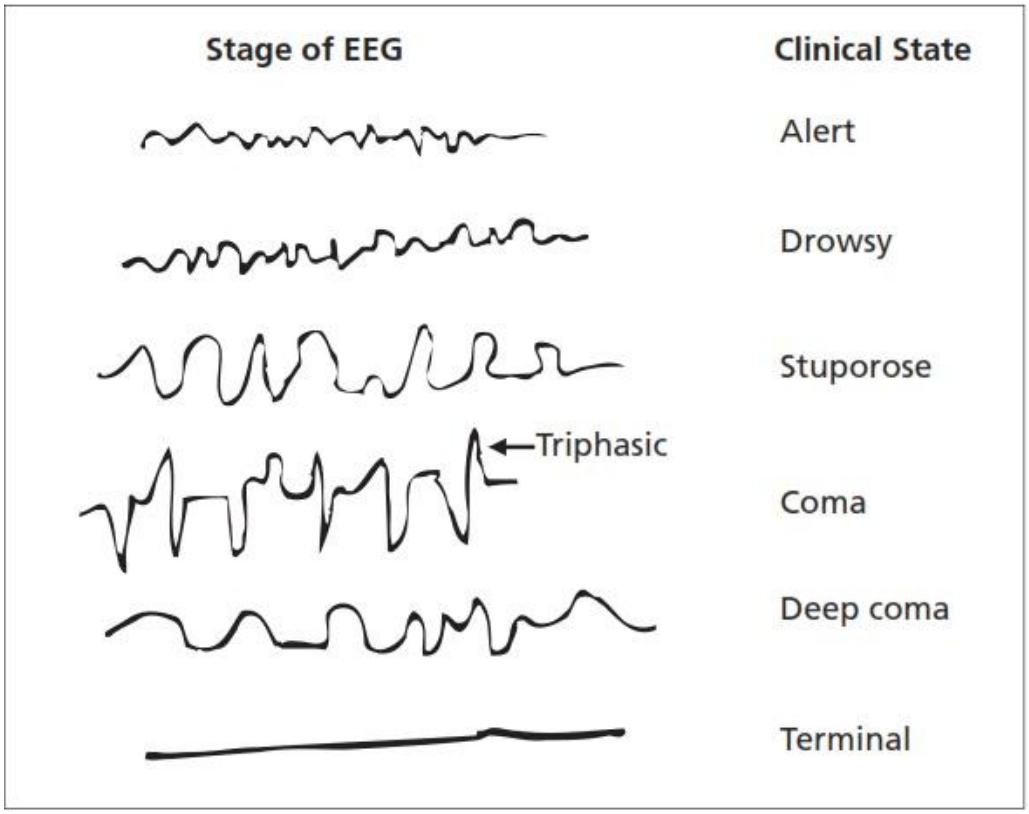
ELECTROPHYSIOLOGICAL ASSESMENTS:

CRITICAL FLICKER FREQUENCY TEST:

From 2002 this test is being used to asses patients with HE .this test was used on the principle of hepatic retinopathy. The retinal glial cells undergo swelling as cerebral glial cells swell in patients with HE .Light impulses are showed at a frequency of 60 Hz and gradually reduced by 0.1 Hz once per second .the frequency at which light impulses are first perceived is the critical flicker frequency. The frequency below 39 Hz detects minimal hepatic encephalopathy with high specificity, sensitivity. This test correlates strongly with paper and pencil neuropsycometry test.

ELECTROENCEPHALOGRAPHY

For research purposes this is an excellent tool for detecting hepatic encephalopathy. Brains electrical activity is decreased in HE. Common findings are increase in wave amplitude and decrease in wave frequency. First theta waves [4-7cps] occurs then delta waves [1-3cps] occurs. Then there will be loss of wave amplitude and flattening of curve occurs. This is mainly used for follow up examinations .clinical improvement is preceeded by increase in EEG frequency. This is associated with variable sensitivity for diagnosis of HE. Spectral EEG can be also used.



EEG changes in patients with cirrhosis with increasing deterioration in neuropsychiatric status. There is an initial slowing in frequency with increasing amplitude. The amplitude then decreases. Finally there is an absence of rhythmic activity.

EVOKED POTENTIALS

This is subdivided into exogenous and endogenous evoked

Potentials .exogenous evoked potentials consists of

- 1.visual evoked potentials[VEP]
- 2.brainstem auditory evoked potentials[BAEP]
- 3. Somatosensory evoked potential.

These are used to assess sensory pathways. Among these BAEP is sensitive to diagnose HE.

Endogenous evoked potentials asses the cognitive function P300 wave is commonly used in this.P300 represents stimulus evaluation processing.

Latency –stimulation evaluation time

Amplitude –meaning of the evoking stimulus within the experimental task.

The acoustic oddball experiment is used in this.by ear phone two tones are randomly presented to patient ear.

Target tone-the patient has to press the button if he hears rare tone.

Standard tone-the patient has to ignore the button if he hears the frequent tone.

In this 150 tones are presented in which 20% are target tones. During this process

EEG is recorded continuously. Then separately average for target and standard tones. The P300 latency is prolonged in patients with HE.

Newer advances in EEG are dominant activity and cluster analysis, artificial neural network expert system software and short epoch.

BRAIN IMAGING:

CT brain:

Identifies conditions that mimic or worsen HE, such as cerebrovascular event or Subdural hematoma.it is used for excluding other causes of encephalopathy.

In most patients with HE it poorly detects low grades of cerebral edema.it is associated with risk of radiation exposure.

MRI brain:

Multiple techniques are available. Identifies several brain abnormalities associated with HE.

T1-weighted imaging:

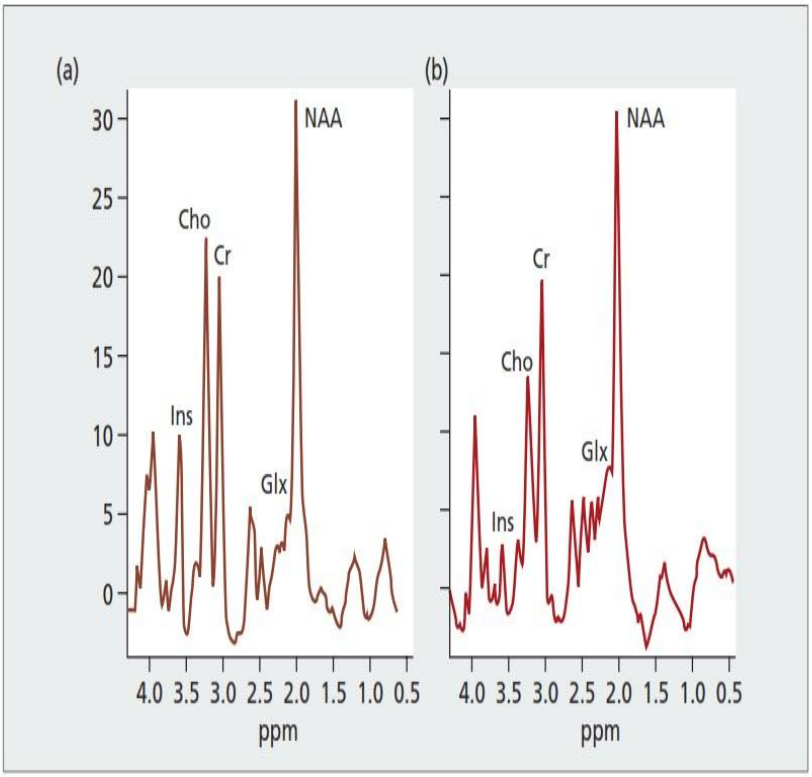
This identifies bilateral symmetrical high intensity signal in the basal ganglia, due to deposition of manganese.it is identified in patients with cirrhosis with Porto Systemic shunts .this reverses after liver transplantation.

T2-weighted FLAIR SEQUENCE and diffusion weighted imaging:

This identifies diffuse increase in white matter signal intensity in the cerebral hemispheres and the corticospinal tract .this is due to cerebral edema and this explains the neurologic abnormalities in cirrhotic patients. This reverses after liver transplantation.

MR spectroscopy:

This identifies increase in glutamate and glutamine signals, decrease in myoinositol and choline signals .homeostatic compensatory metabolic changes occur in the astrocyte of cirrhotic patients that prevent massive cerebral edema. This also resolves after liver transplantation.



H-MR-spectroscopy water-suppressed spectra in a healthy individual (a) and in a patient with cirrhosis and hepatic encephalopathy (b) recorded with a stimulated echo acquisition mode pulse sequence (TR/TE, 1600/20 ms; acquisitions, 256). The main resonances correspond to *N*-acetylaspartate (NAA: 2.0 ppm), glutamine/ glutamate (Glx, 2.1–2.5 ppm), creatine/ phosphocreatine (Cr: 3.02 ppm), choline-containing compounds (Cho: 3.2 ppm) and myoinositol (Ins: 3.55 ppm). The presence of hepatic encephalopathy is characterized by a relative increase in the glutamate/ glutamine resonance and relative reductions in the myoinositol and choline resonances.

Magnetic transfer ratio:

This identifies mild diffuse reduction in magnetic transfer ratio in white matter.it reflects mild cerebral edema. These imaging modalities and regional cerebral blood flow changes are useful in understanding the pathogenic mechanisms and at present are not considered of diagnostic value.

CLINICAL SIGNIFICANCE:

EFFECT OF MHE ON HEALTH RELATED QUALITY OF LIFE:

MHE patients have a minimal Impairment in cognition many times. They have abnormalities in sleep, poor memory, impaired psychomotor performance and decreased attention. Activities involving these domains like planning a trip, driving a car are affected. These abnormalities affects their capacity in workplace and they have socioeconomic problems. They also won't have regular employment.by using HRQoL questionnaire it has been found that cirrhotic patients with MHE have higher frequency of sleep disorders. they have unsatisfied sleep like increased daytime sleepiness, increased sleep latency, increased awakening episodes during night and decreased sleeping time .they also have defective memory. They are also defective in visual perception. They also have deficit in short term memory with relatively normal long term memory.

EFFECT OF MHE ON DRIVING:

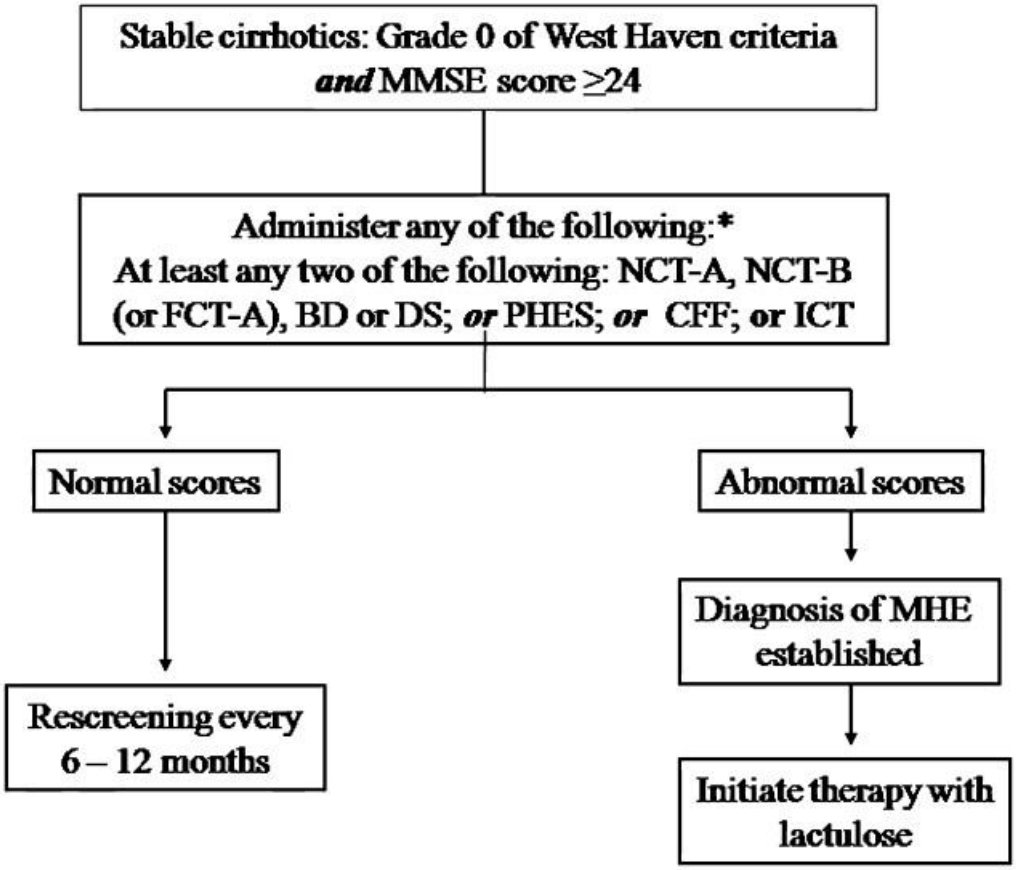
In a study conducted by wein and colleagues it was found that in a standardized 90 minute on the road driving test 36% of cirrhotic patients with MHE had impairment in driving a car. Due to impaired cognition they are at increased risk of automobile accidents. They also had higher traffic rule violations.in unexpected traffic conditions they had decreased

speed of mental processing. Navigation is very important in driving.it is impaired in these patients and so they won't have response inhibition and driving.it has been found that persons who perform poorly inhibitory control test are more prone for illegal turns and accidents.

TREATMENT:

It consists of

- 1. Pharmacologic therapy
- 2.nutritional interventions
- 3. Long term management.



PHARMACOLOGIC THERAPY:

Identification of the precipitating factor and treating it helps in relieving the symptoms. The basic idea in treating is to decrease the production of ammonia and decreasing the absorption of ammonia.

NON- ABSORBABLE DISACCHARIDES:

These include lactulose and lactitol. Studies have shown that these agents improve cognitive function, health related quality of life and

sickness impact profile. This is the ‘first line’ therapy for HE. The oral dosage is 15 – 30 ml two times a day to produce 2 – 3 soft stools daily. This acts as a laxative and decreases colonic pH, which decreases the glutamine uptake in the gut and decreases the production and absorption of ammonia.

Adverse effects:

- Abdominal bloating
- Hyponatremia
- Dehydration
- Sweet taste in the mouth.

ANTIBIOTICS:

Neomycin was initially used in treating HE patients. This reduces ammonia level by inhibiting mucosal glutaminase in the gut.it inhibits growth of ammoniagenic coliform bacteria. Due to safer antibiotics its use has declined. Its adverse effects are intestinal malabsorption, ototoxicity and nephrotoxicity.

Rifaximin is a safer antibiotic with few side effects.it was approved by FDA in March 2010 for treating HE. Its oral dose is 550 mg two times daily.in studies it was shown that remission of HE was prolonged in patients on rifaximin treatment.

PREBIOTICS AND SYNBIOTICS:

These agents decreases intestinal pH and decreases ammonia production and decreases portal blood ammonia levels. These synbiotics increases non urease producing lactobacillus species and decreases urease producing E.coli .patients taking probiotic yogurt a palatable food had showed improvement in psychometric tests .this is a effective, safe and long term therapy for MHE patients. This is commonly available food item.

Other pharmacological agents that can be used are zinc, bromocritine, L-ornithine

L-aspartate.

NUTRITIONAL INTERVENTIONS:

Skeletal muscle metabolizes ammonia.in cirrhotic patients due to lean body mass this path is affected and ammonia level increases in brain.

Cirrhotic patients should take 1.2 g/kg of protein daily that should be supplemented with vegetable protein and BCAA.

BCAA:

These amino acids improve serum albumin levels. Patients on BCAA recovers soon from HE, and they have increased progression free survival. BCAA also decreases number of hospital admissions and decreases the duration of stay.

VEGETABLE BASED PROTEIN:

Vegetable protein decreases colonic pH and decreases ammonia level.it has high fibre content and increases colonic motility and increases clearance of intestinal nitrogen.

LONG TERM MANAGEMENT:

OUTPATIENT MANAGEMENT:

After patients have recovered from an episode of HE, they have to be on long term empiric therapy. Because this helps in good quality of life and recurrences can be prevented. Long term therapy mainly comprises lactulose and rifaximin .patients should be educated about their bowel movements and stool consistency and titration of lactulose .rifaximin is safe and patients maintaining their remission effectively.

SURVIVAL:

MHE severely affects survival of cirrhotic patients. Those who are having poor liver function, abnormal PHES score and abnormal child Pugh score had poor prognosis. Patients with MHE tend to have more frequent overt HE.

PROGNOSIS:

Patients with MHE may improve, remain unchanged, deteriote or develop overt HE. Patients with severe liver dysfunction, abnormal PHES score,CFF >38,abnormal child Pugh score have more chances to develop overt HE.

PSYCOMETRIC HEPATIC ENCEPHALOPATHY SCORE:

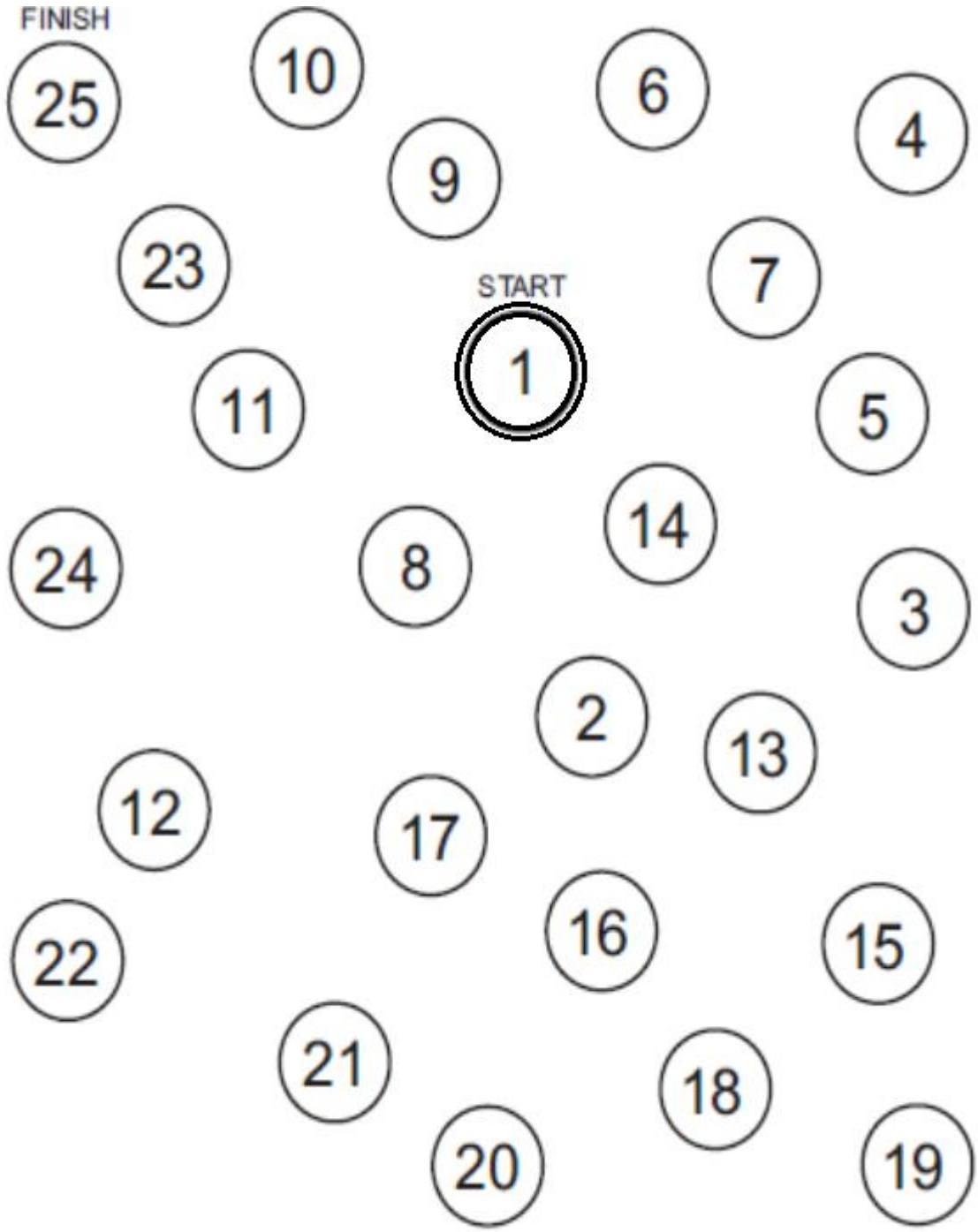
This includes number connection test –A, number connection test – B, digit symbol test [DST], Line drawing test, circle dotting test. Impairment of >2 SD in two or more tests is needed to diagnose minimal hepatic encephalopathy.

NUMBER CONNECTION TEST – A:

Purpose: this measures visuospatial orientation and psychomotor speed.

Description: the subject is shown a paper with 25 numbered circles spread randomly. The test is to connect 1-25 as quick as possible.

Scoring : score is the time needed to complete with error correction.

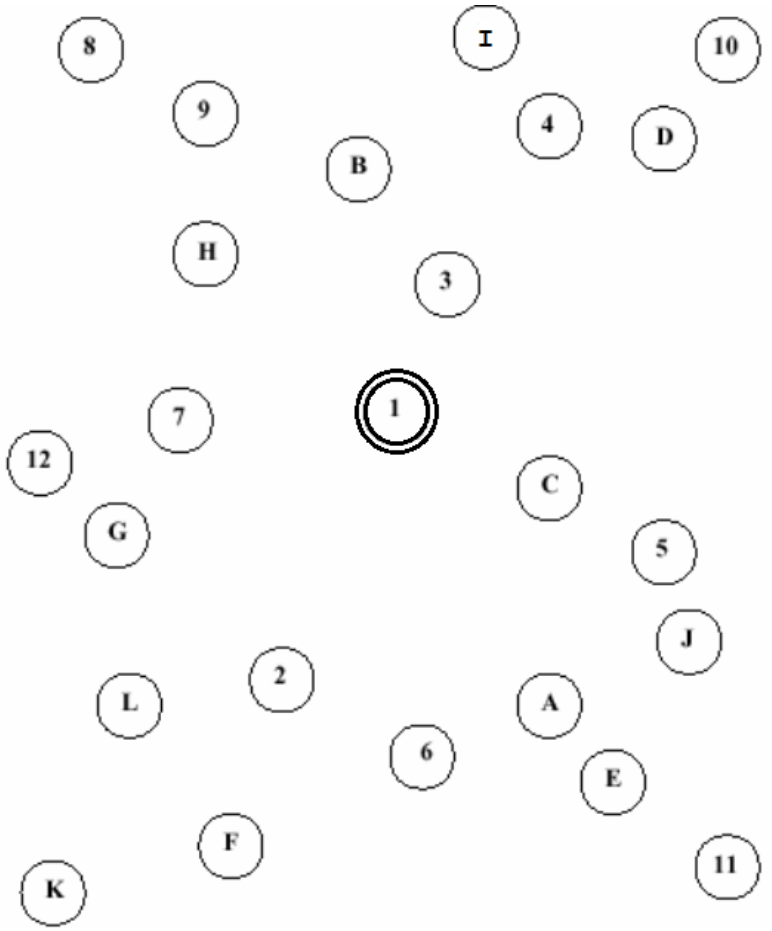

FINISH
25
10
6
4
9
23
START
7
1
11
5
14
24
8
3
2
13
12
17
16
15
22
21
18
20
19

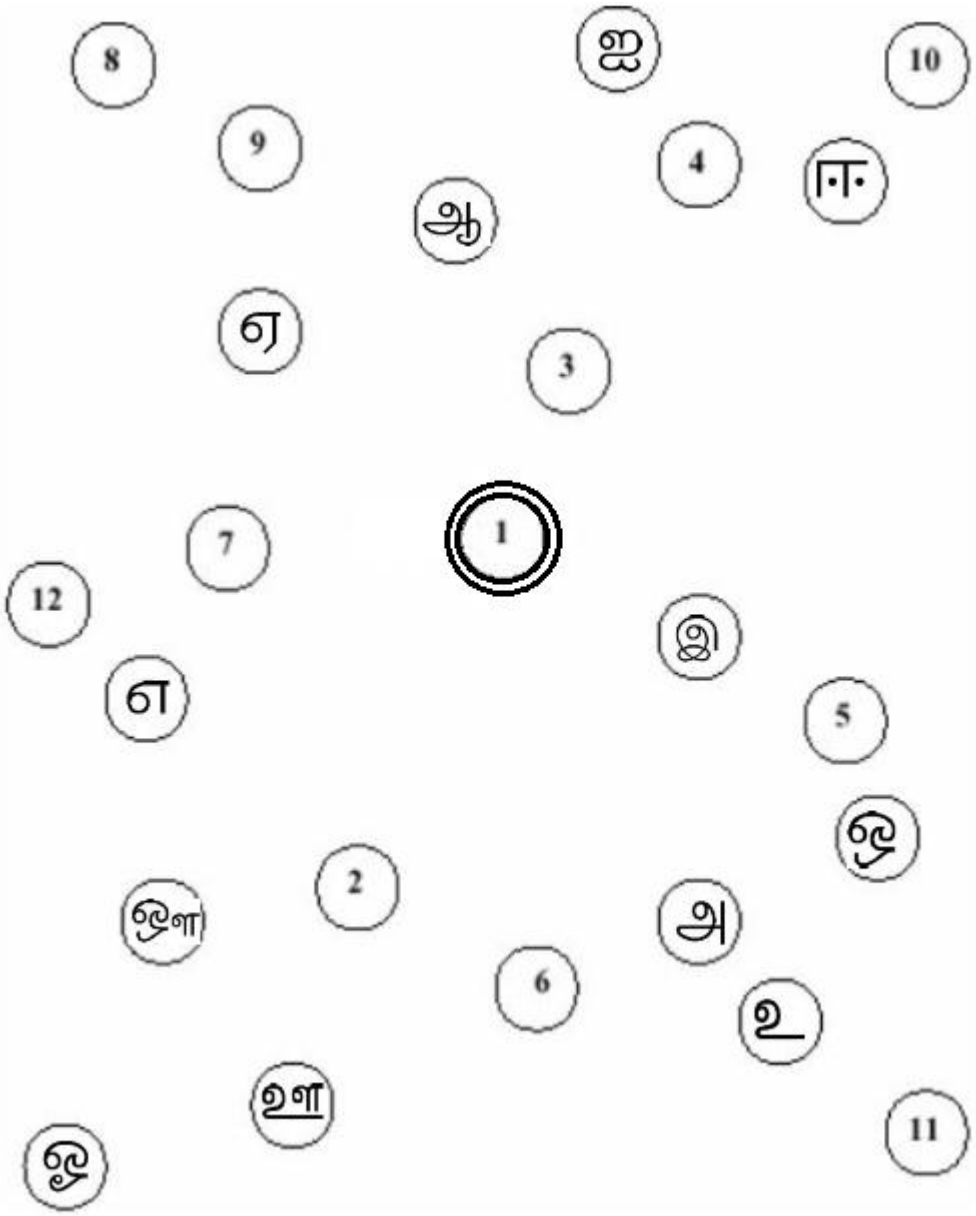
NUMBER CONNCTION TEST –B:

Purpose: this measures visuospatial orientation, psychomotor speed, ability to shift attention.

Description: this test contains numbers 1 – 13 and letters from A – L. subject is asked to connect numbers and letters in alternating manner .that is from 1-A-2-B-3-C and so on.

Scoring: time needed to complete with error correction.




8
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10
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3
1
7
12
இ
எ
5
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2
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6
உ
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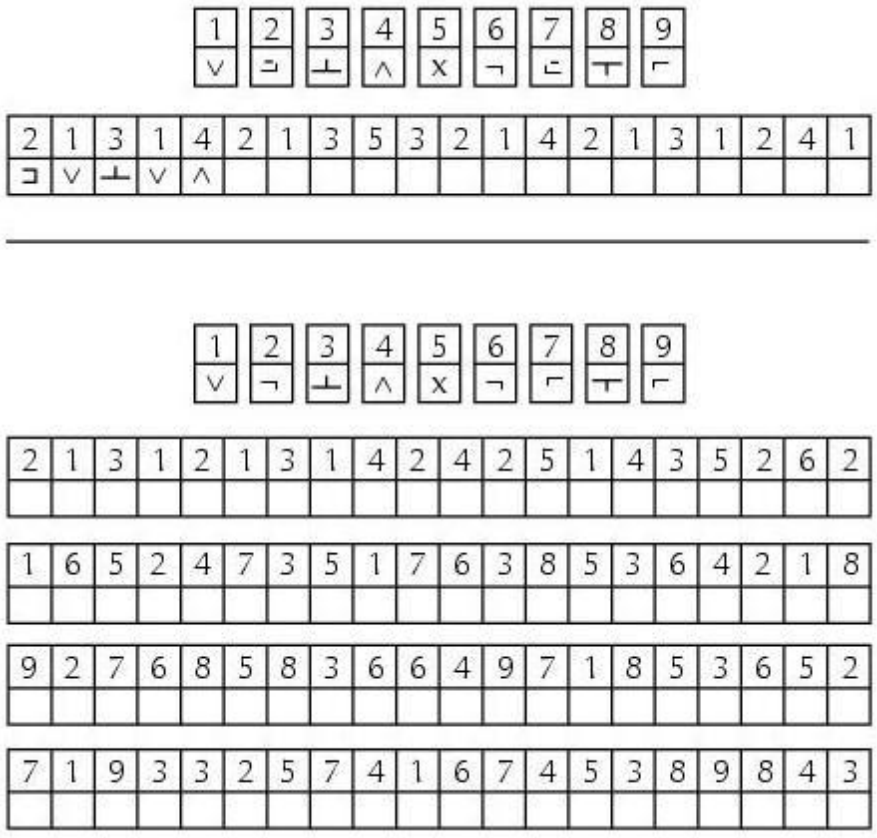
11
ஒ

DIGIT SYMBOL TEST :

Purpose: this measures visuo constructive abilities.

Description: this test contains double boxes in which numbers are given in upper part and in the lower part the subject is to draw symbols pertinently.

Scoring: result is number of boxes correctly filled within 90 seconds.

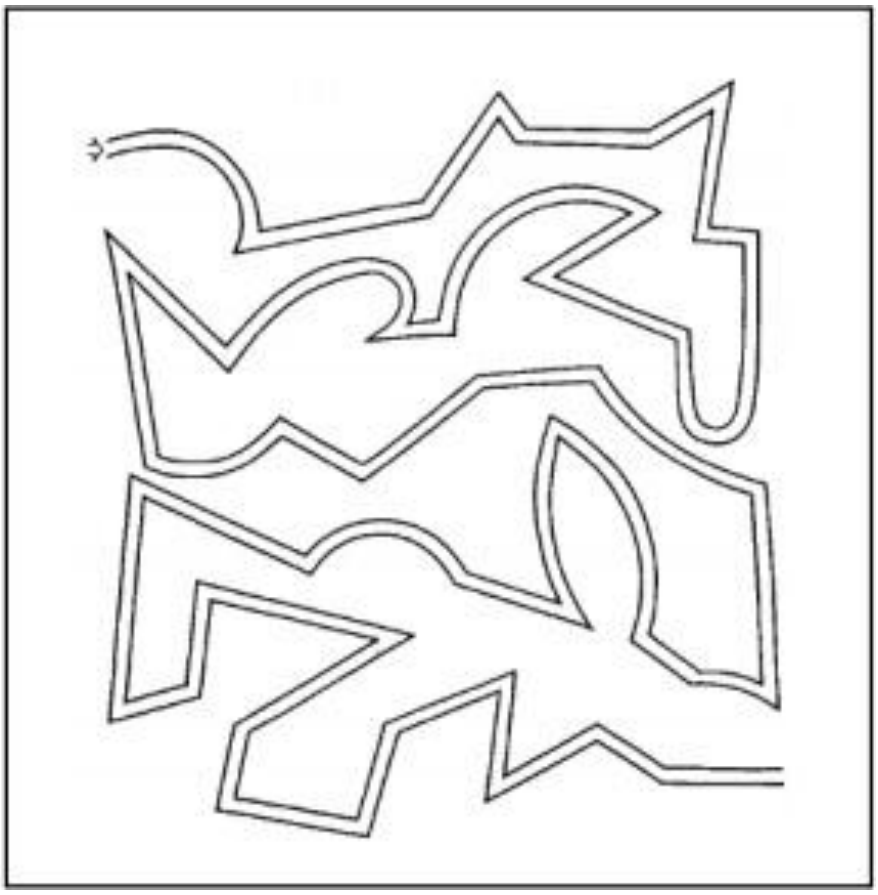


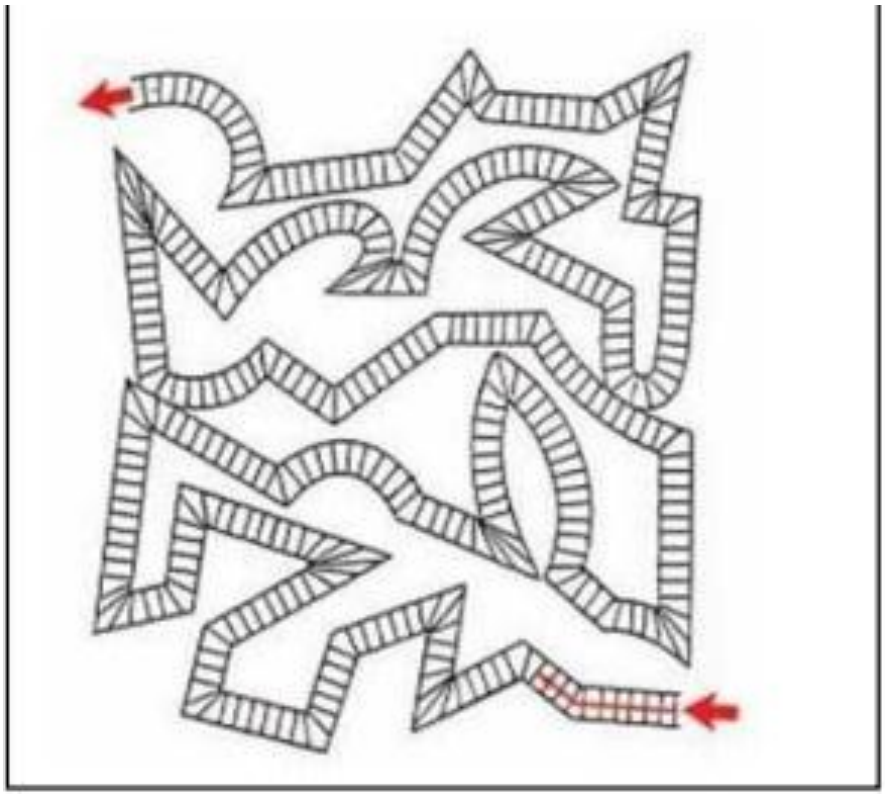
LINE DRAWING TEST:

Purpose: this measures motor speed and accuracy.

Description: the subject has to follow the route of labyrinth without touching the borderline and crossing. For assessing whole route is divided into small sections and each touching or crossing the border in a section is noted.

Scoring: time needed to go through the labyrinth and number of mistakes.





CIRCLE DOTTING TEST:

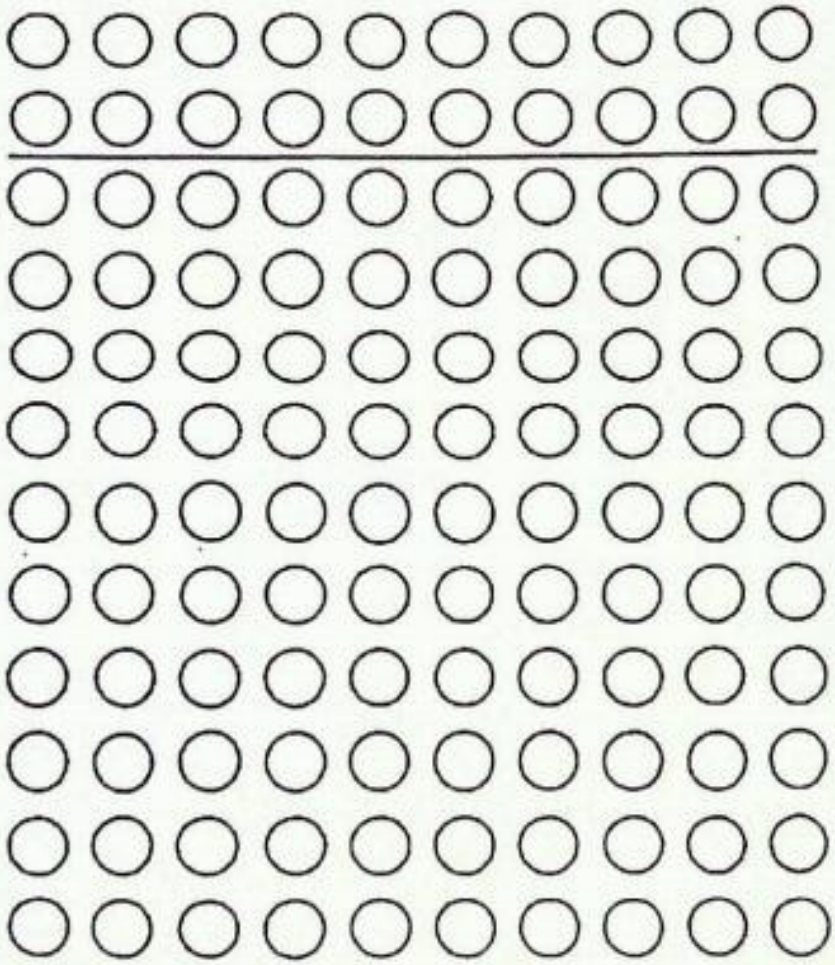
Purpose: tests pure motor speed.

Description: the subject has to put a dot in each of 100 circles given on the sheet.

Scoring: time needed to complete.

Testblatt Kreise punktieren (KP)

Name: Alter:
Testdatum: _____ Erhebungsort: _____



MATERIALS & METHODS

MATERIALS AND METHODS

SOURCE OF DATA:

Patients admitted in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 diagnosed to have Cirrhosis of liver, fulfilling the inclusion and exclusion criteria were included in the study group.

SAMPLE SIZE:

40 cases and 40 controls

STUDY DESIGN:

Case – control study

STUDY DURATION:

6 months: March 2014-August 2014

INCLUSION CRITERIA:

- Age > 18 years
- Confirmed cirrhotic patients

EXLUSION CRITERIA:

Healthy volunteers	Cirrhotic patients
1.presence of psychiatric/neurological disorders 2.consumption of psychotropic drugs 3.alcohol consumption of >50g/d within past 3 months 4.inability to read and write	1.history of overt hepatic encephalopathy 2.consumption of lactulose/psychoactive drugs/any antibiotics during the past two weeks 3.presence of psychiatric/neurological disorders 4.consumption of alcohol >50g/d within past 3 months 5.inability to read and write

DATA COLLECTION AND METHODS:

Patients have their history taken according to a questionnaire and subjected to clinical examination and investigations.

- All five tests of PHES were administered to all the enrolled subjects in the same sequence. The test were conducted on a one to one basis in a quiet room with sufficient light.
- Liver function tests
- Serum ammonia
- Ultra sound abdomen
- EEG

STASTICAL METHODS APPLIED:

Datas were analysed using the SPSS software. Statistical significance was indicated by the Chisquare test. Variables were considered to be significant if $p<0.05$

OBSERVATION

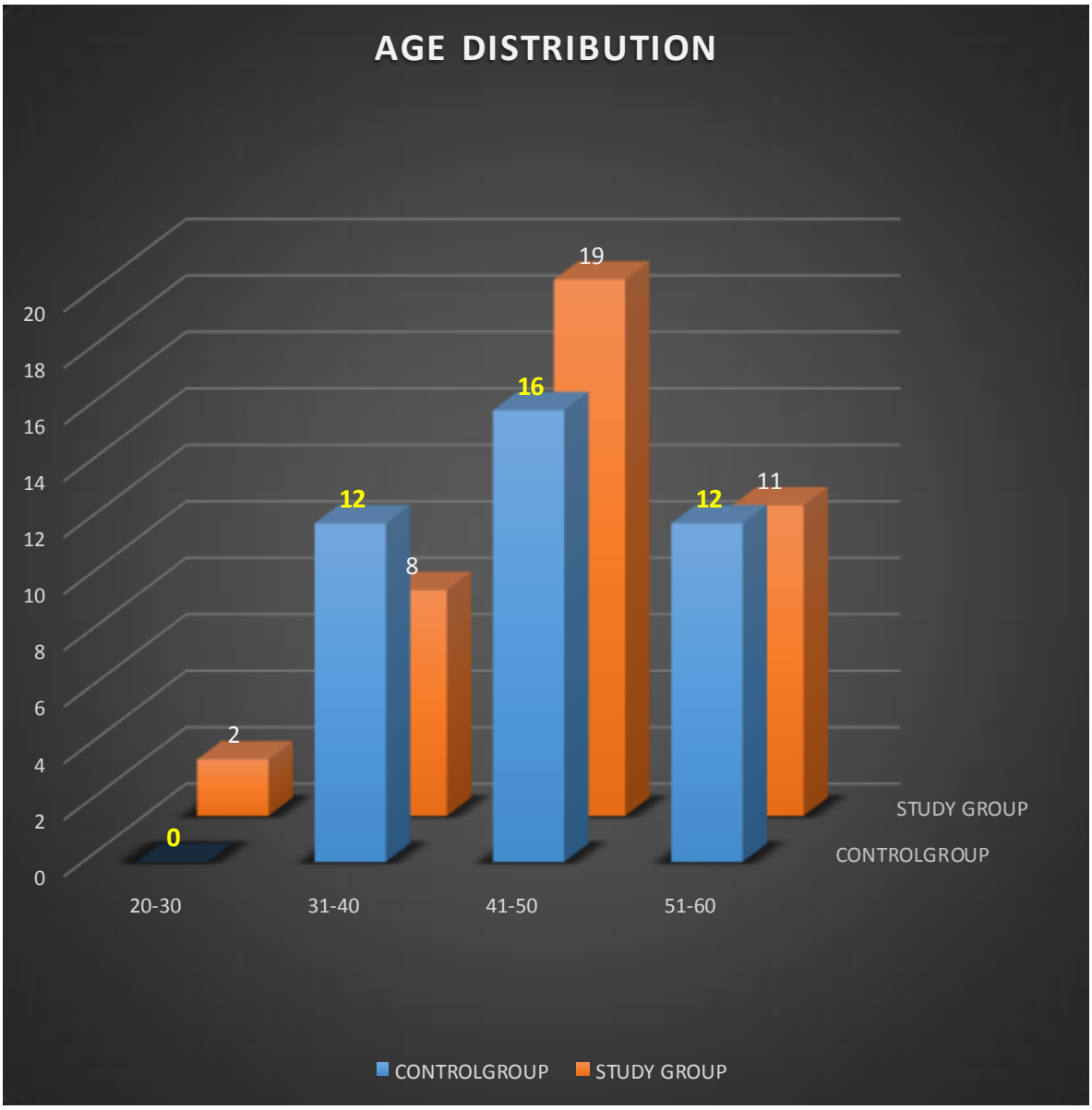
&

RESULTS

OBSERVATION AND RESULTS

AGE DISTRIBUTION

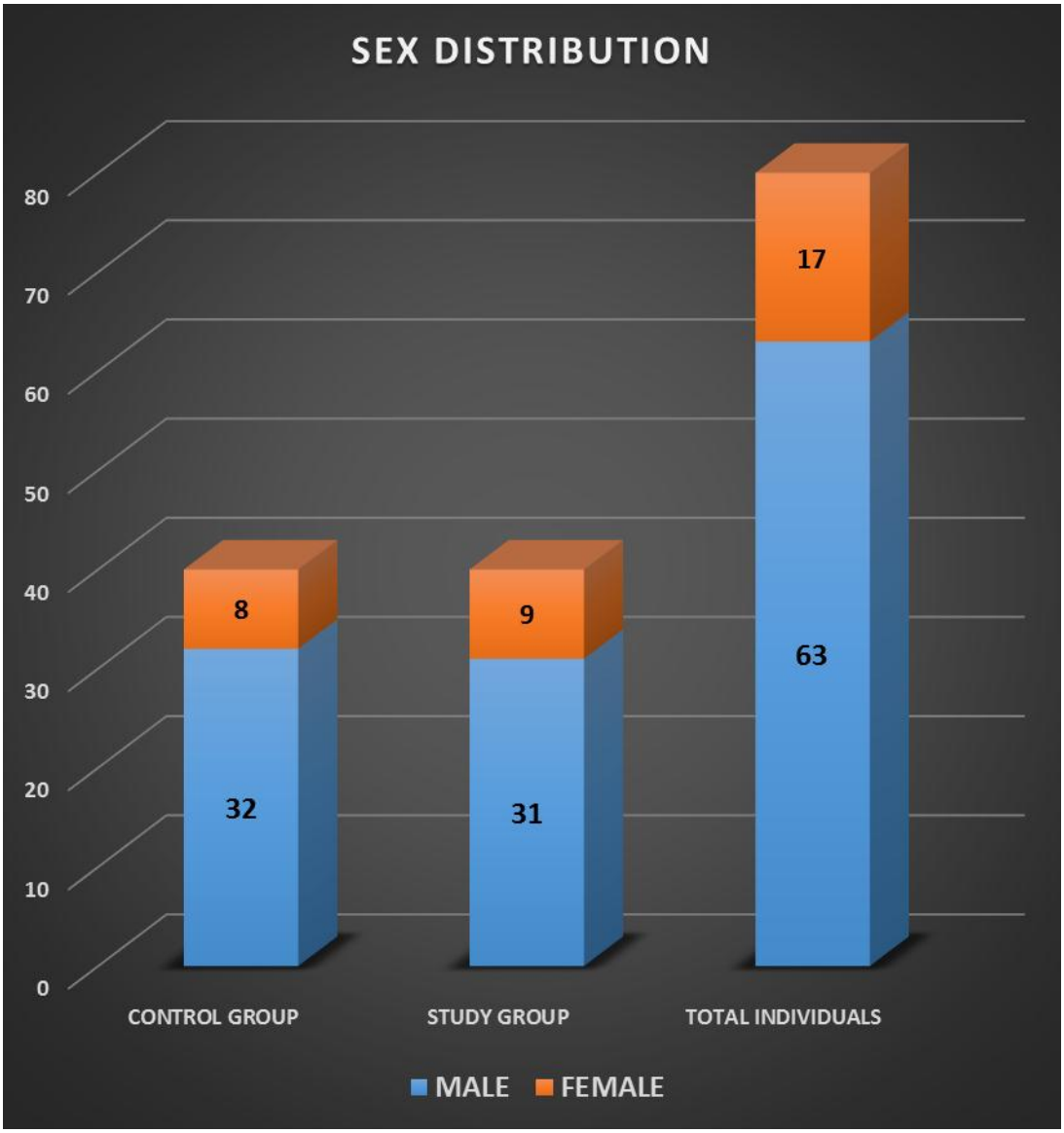
AGE	CONTROL GROUP	STUDY GROUP
20-30	0	2
31-40	12	8
41-50	16	19
51-60	12	11
TOTAL	40	40


AGE DISTRIBUTION
20
18
16
14
12
10
8
6
4
2
0
0
2
12
8
16
19
12
11
20-30
31-40
41-50
51-60
STUDY GROUP
CONTROLGROUP
CONTROLGROUP
STUDY GROUP

SEX DISTRIBUTION:

GROUP		MALE	FEMALE	TOTAL
CONTROL	COUNT	32	8	40
	%WITHIN GROUP	80%	20%	100%
	%WITHIN SEX	50.8%	47.1%	50%
CASES	COUNT	31	9	40
	%WITHIN GROUP	77.5%	22.5%	100%
	%WITHIN SEX	49.2%	52.9%	50%
TOTAL	COUNT	63	17	80
	%WITHIN GROUP	78.8%	21.3%	100%
	%WITHIN SEX	100%	100%	100%

SEX DISTRIBUTION



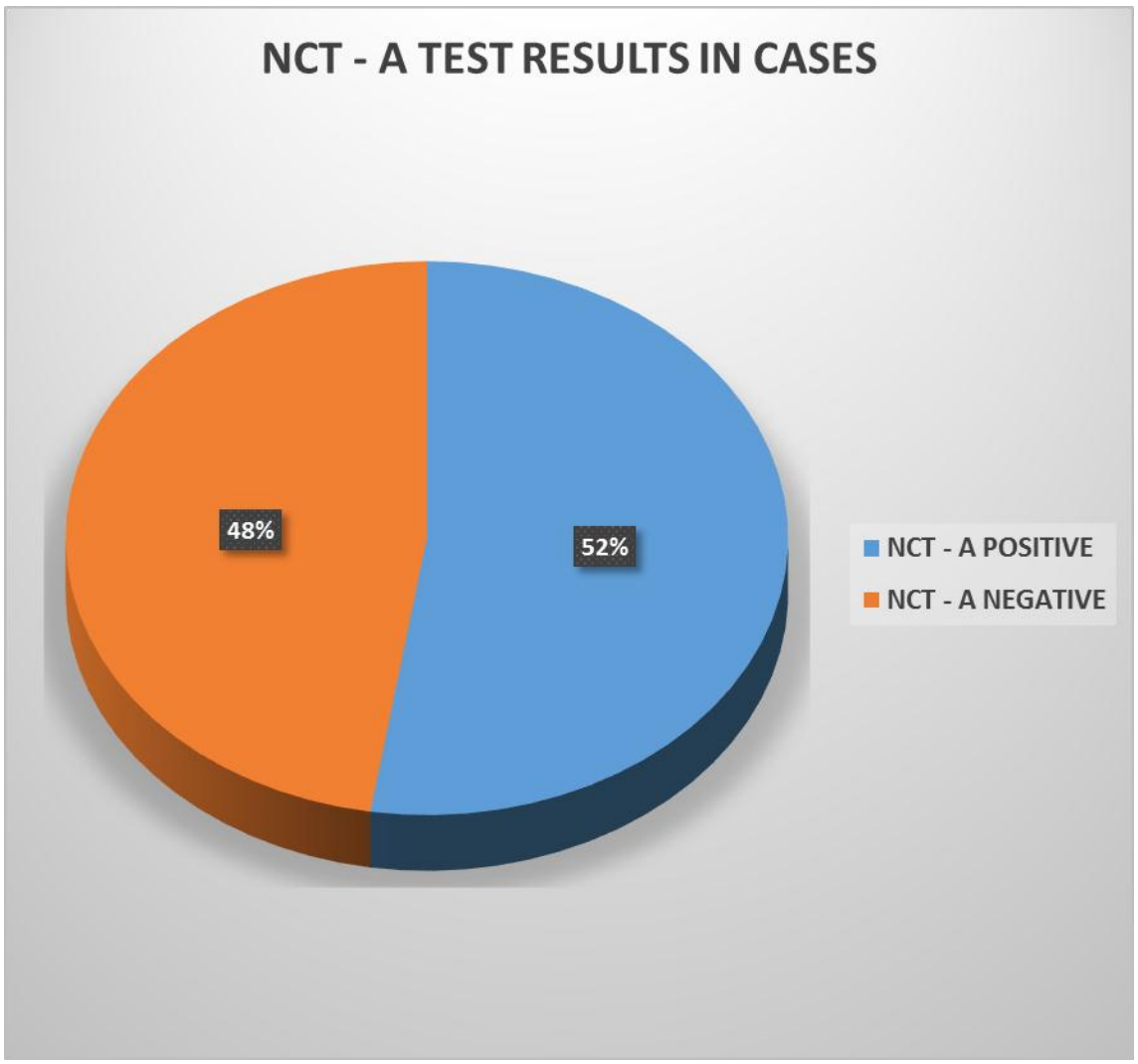
NCT – A

GROUP	NUMBER OF INDIVIDUALS	MEAN	SD	STANDARD ERROR MEAN	P value
CONTROLS	40	65.63	9.599	1.518	0.000
CASES	40	77.28	15.436	2.441	

P value <0.001 – highly significant

NCT – A	CASES	
	NUMBER OF INDIVIDUALS	% WITHIN THE GROUP
POSITIVE	21	52.5
NEGATIVE	19	47.5

NCT – A


NCT - A TEST RESULTS IN CASES
48%
52%
NCT - A POSITIVE
NCT - A NEGATIVE

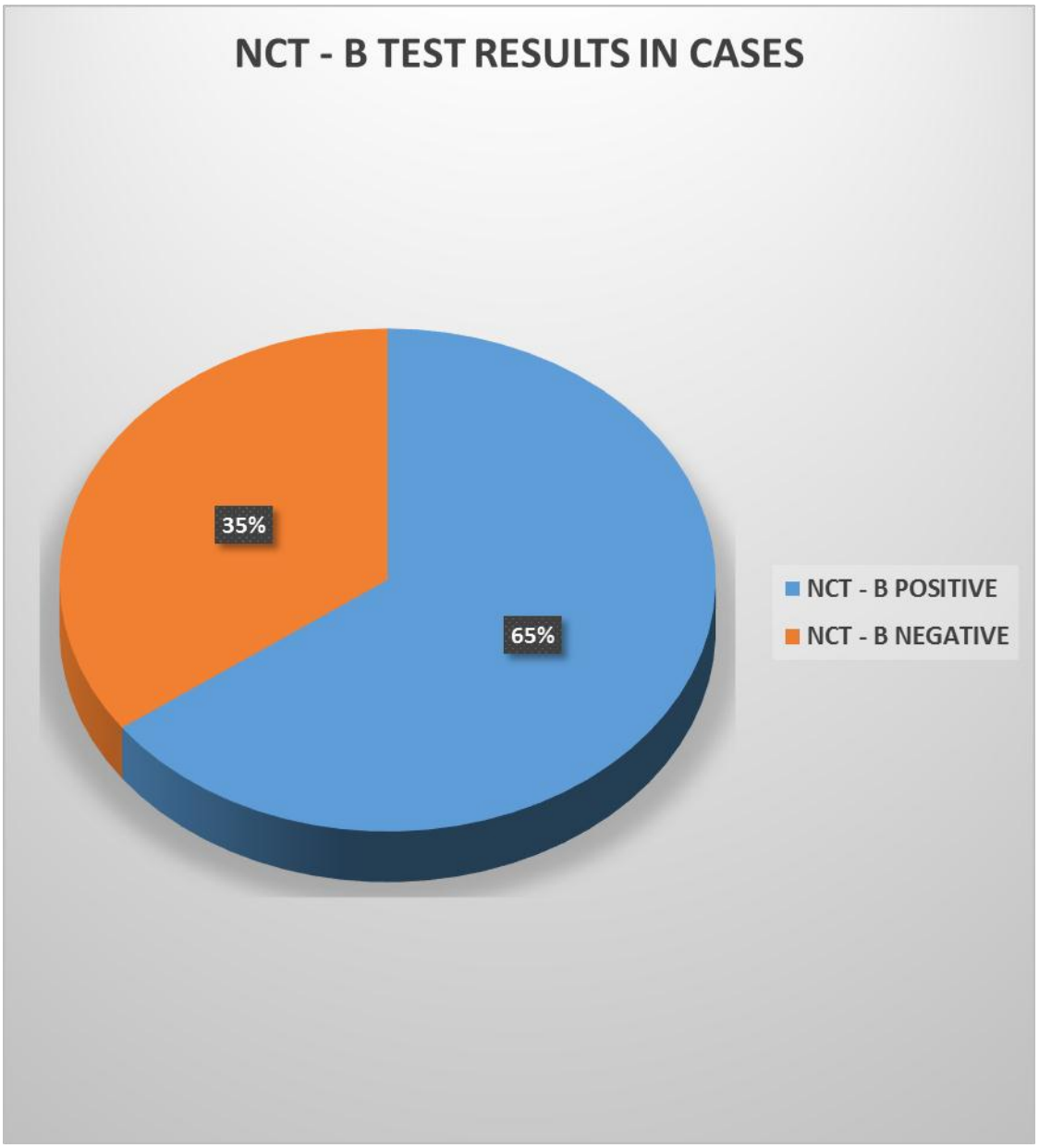
NCT – B

GROUP	NUMBER OF INDIVIDUALS	MEAN	STANDARD DEVIATION	STANDARD ERROR MEAN	P value
CONTROLS	40	91.80	10.528	1.665	0.000
CASES	40	115.05	35.682	5.642	

P value < 0.001 – highly significant

NCT – B	CASES	
	NUMBER OF INDIVIDUALS	% WITHIN THE GROUP
POSITIVE	26	65
NEGATIVE	14	35

NCT – B


NCT - B TEST RESULTS IN CASES
35%
65%
NCT - B POSITIVE
NCT - B NEGATIVE

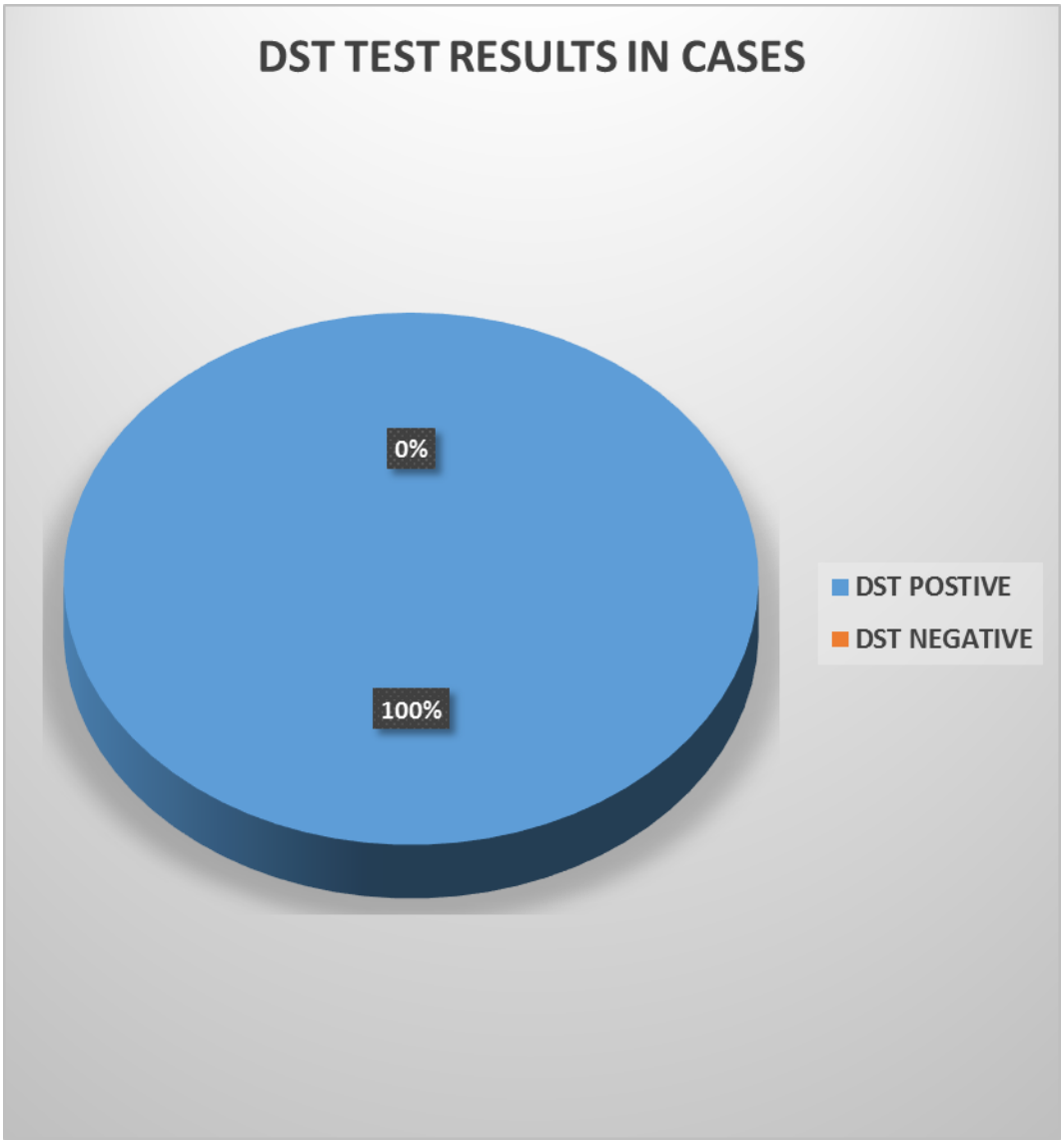
DST

GROUP	NUMBER OF INDIVIDUALS	MEAN	STANDARD DEVIATION	STANDARD ERROR MEAN	P value
CONTROLS	40	24.65	4.389	0.694	0.000
CASES	40	17.83	5.879	0.929	

P value < 0.001 – highly significant

DST	CASES	
	NUMBER OF INDIVIDUALS	% WITHIN THE GROUP
POSITIVE	40	100
NEGATIVE	0	0

DST



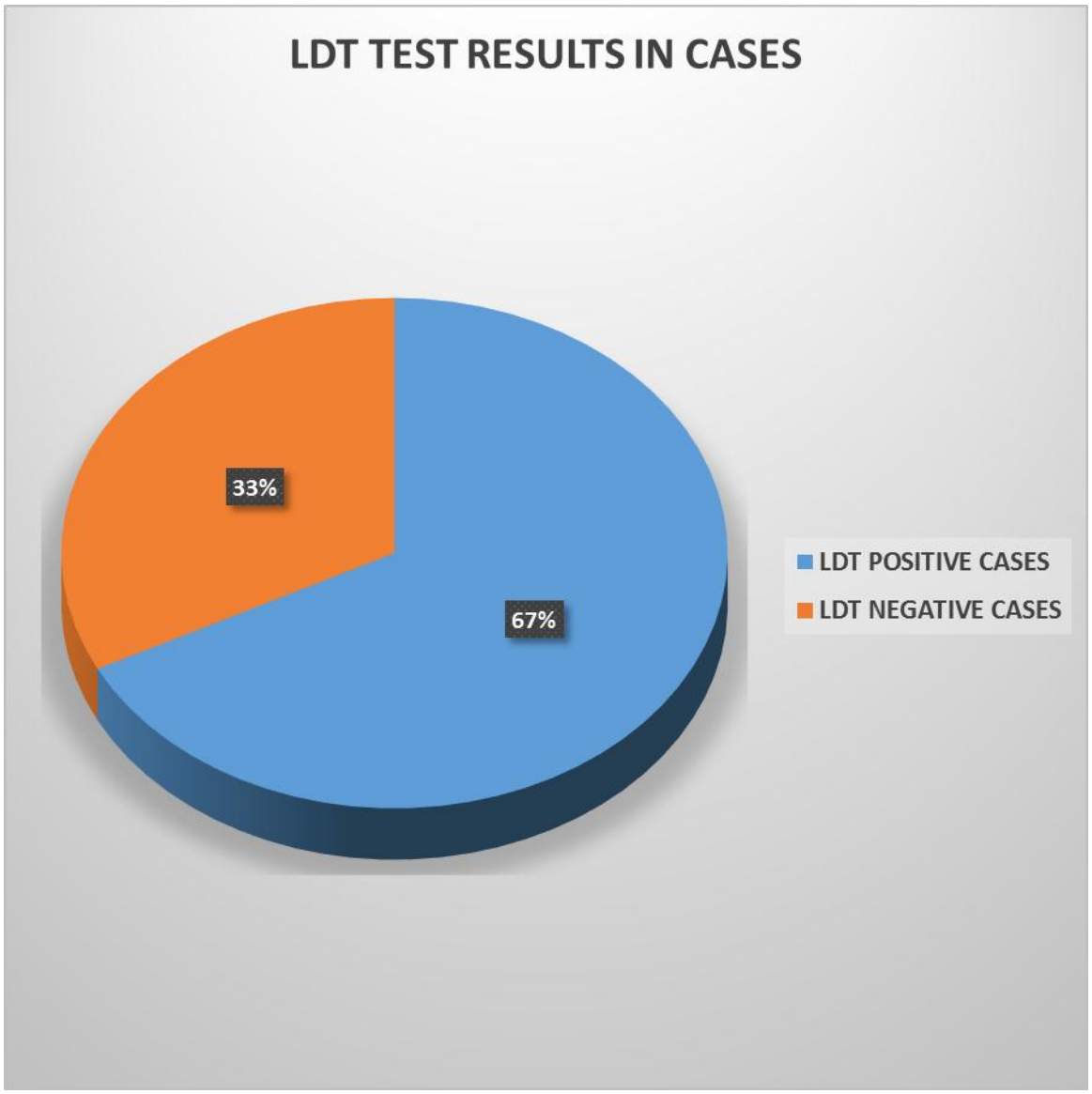
LDT:

GROUP	NUMBER OF INDIVIDUALS	MEAN	STANDARD DEVIATION	STANDARD ERROR MEAN	P value
CONTROLS	40	64.03	10.154	1.605	0.000
CASES	40	76.83	15.387	2.433	

P value <0.001 – highly significant

LDT	CASES	
	NUMBER OF INDIVIDUALS	% WITHIN THE GROUP
POSITIVE	27	67.5
NEGATIVE	13	32.5

LDT


LDT TEST RESULTS IN CASES
33%
67%
LDT POSITIVE CASES
LDT NEGATIVE CASES

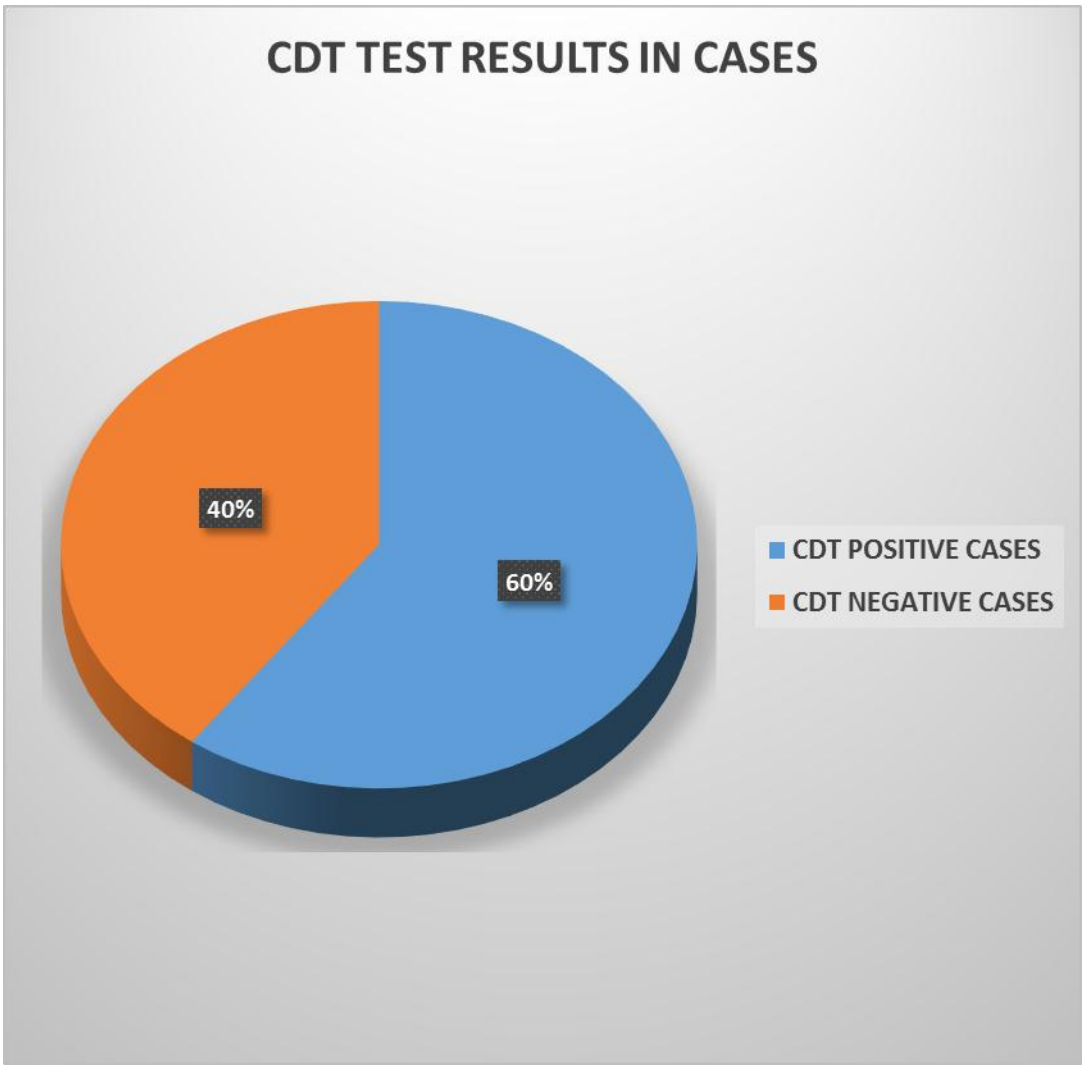
CDT:

GROUP	NUMBER OF INDIVIDUALS	MEAN	STANDARD DEVIATION	STANDARD ERROR MEAN	P value
CONTROLS	40	66.47	8.910	1.409	0.000
CASES	40	79.83	16.175	2.558	

P value <0.001 – highly significant

CDT	CASES	
	NUMBER OF INDIVIDUALS	% WITHIN THE GROUP
POSITIVE	24	60
NEGATIVE	16	40

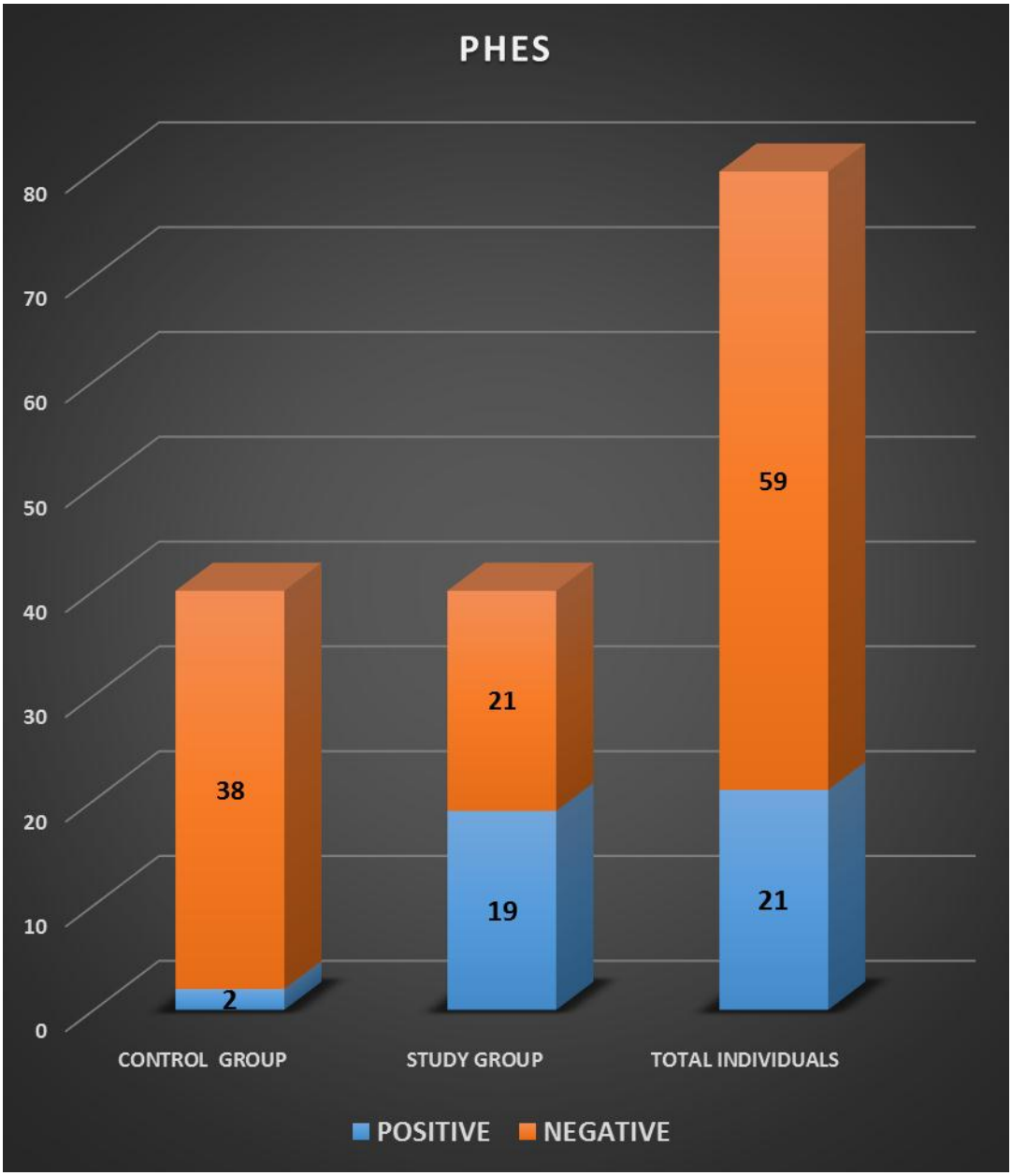
CDT


CDT TEST RESULTS IN CASES
40%
60%
CDT POSITIVE CASES
CDT NEGATIVE CASES

PHES:

GROUP		CONTROL	CASES	TOTAL
POSITIVE	**COUNT**	2	19	21
	%WITHIN PHES POSITIVE	9.5%	90.5%	100%
	%WITHIN GROUP	5%	47.5%	26.3%
NEGATIVE	**COUNT**	38	21	59
	%WITHIN PHES POSITIVE	64.4%	35.6%	100%
	%WITHIN GROUP	95%	52.5%	73.8%
TOTAL	**COUNT**	40	40	80
	%WITHIN PHES POSITIVE	50%	50%	100%
	%WITHIN GROUP	100%	100%	100%

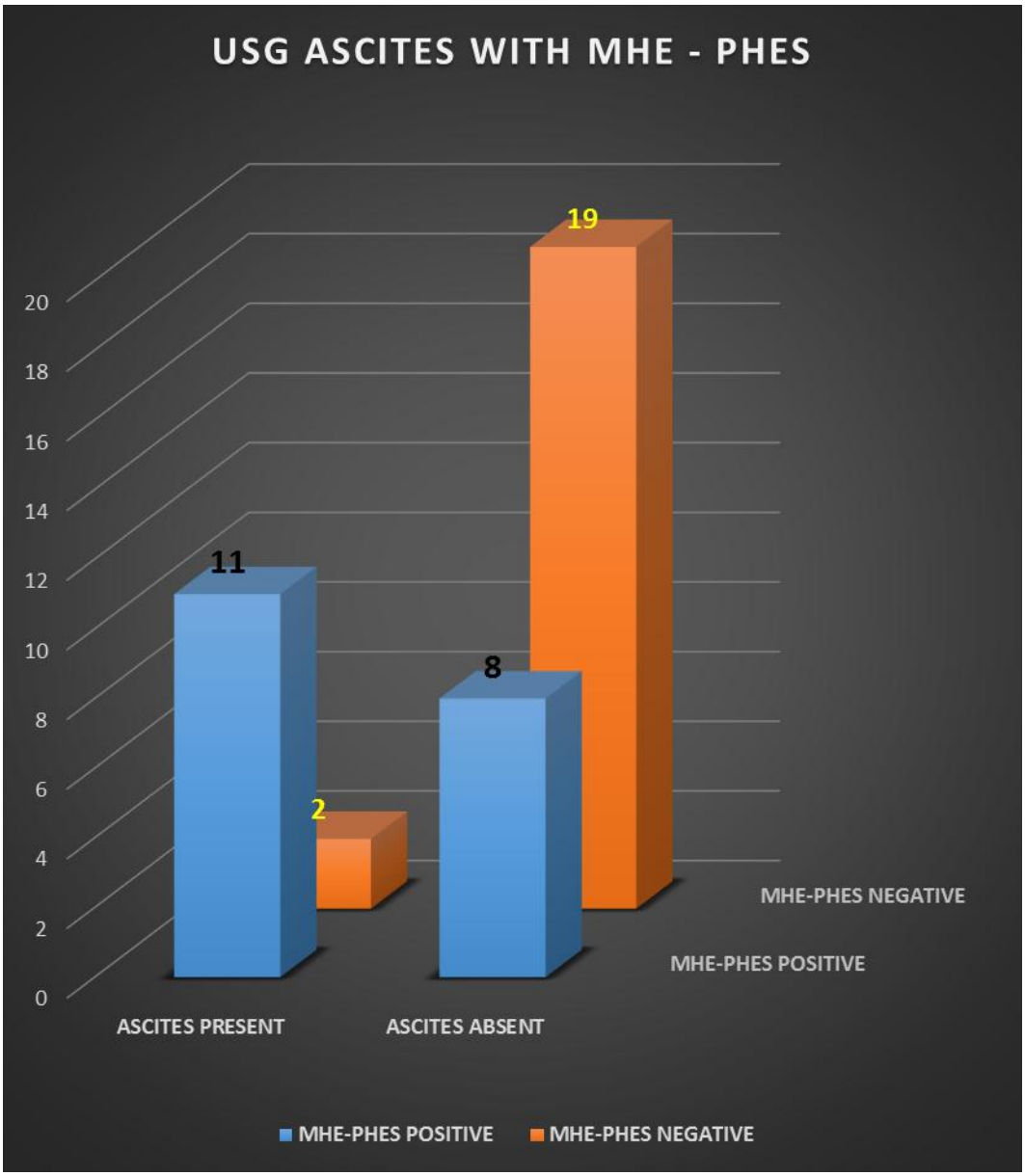
	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	18.660(b)	1	.000		
Continuity Correction(a)	16.529	1	.000		
Likelihood Ratio	20.872	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	18.427	1	.000		
N of Valid Cases	80				


PHES
80
70
60
50
40
30
20
10
0
38
2
21
19
59
21
CONTROL GROUP
STUDY GROUP
TOTAL INDIVIDUALS
POSITIVE
NEGATIVE

USG ASCITES WITH MHE PHES:

USG		**MHE - PHES**	
		POSITIVE	**NEGATIVE**
ASCITES	**PRESENT**	**11**	**2**
	ABSENT	**8**	**19**
TOTAL		**19**	**21**

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.639(b)	1	.001		
Continuity Correction(a)	8.548	1	.003		
Likelihood Ratio	11.374	1	.001		
Fisher's Exact Test				.002	.001
Linear-by-Linear Association	10.373	1	.001		
N of Valid Cases	40				


USG ASCITES WITH MHE - PHES
20
18
16
14
12
10
8
6
4
2
0
11
2
8
19
ASCITES PRESENT
ASCITES ABSENT
MHE-PHES NEGATIVE
MHE-PHES POSITIVE
MHE-PHES POSITIVE
MHE-PHES NEGATIVE

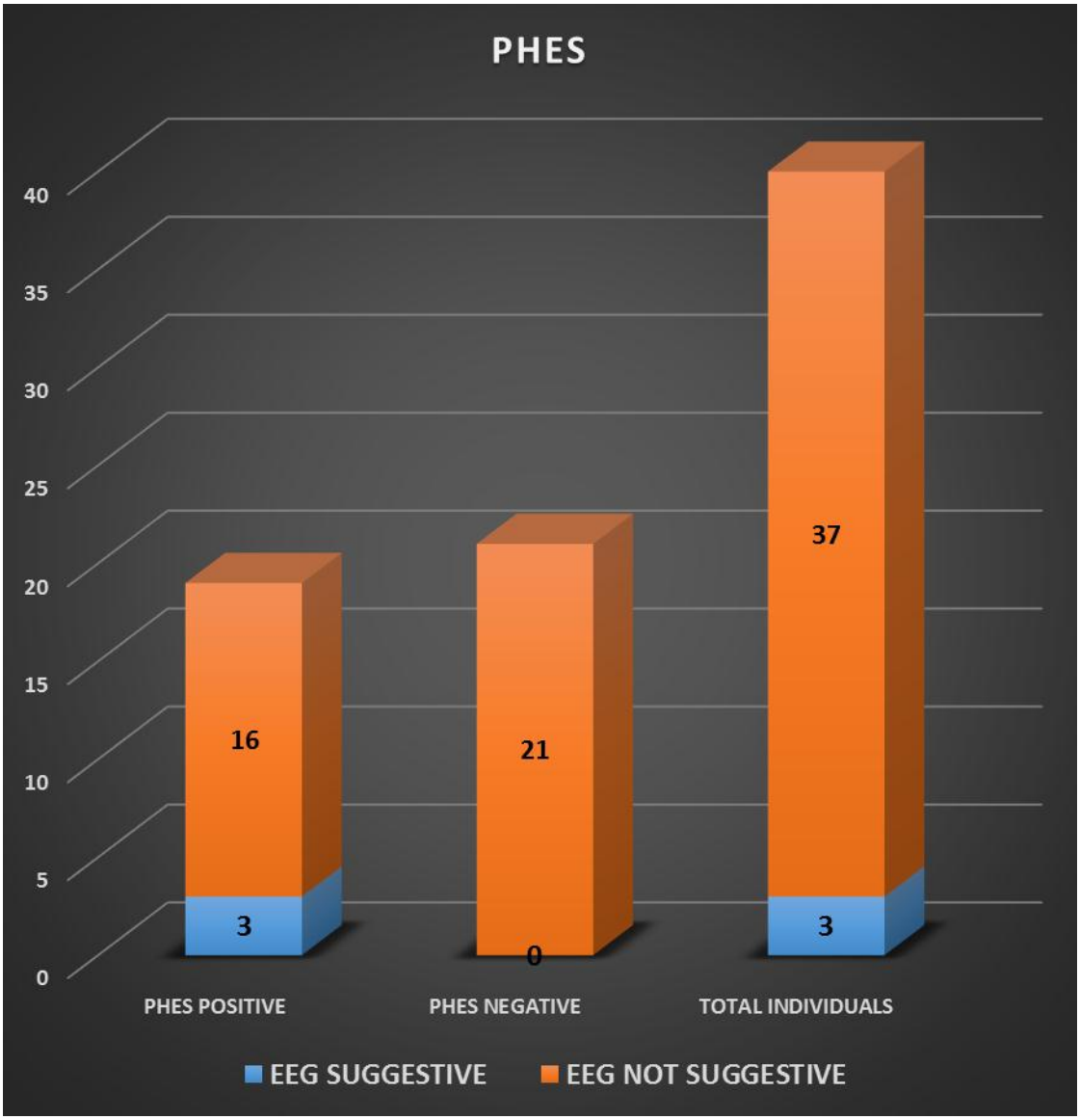
BILIRUBIN AND AMMONIA LEVLES WITH PHES- MHE:

	MHE	NUMBER OF INDIVIDUALS	Mean	Std. Deviation	Std. Error Mean	P value
T.BILIRUBIN	**Positive**	**19**	**5.405**	**3.1914**	**.7322**	**0.001**
	Negative	**21**	**2.681**	**.7387**	**.1612**	
AMMONIA	**Positive**	**19**	**93.47**	**14.615**	**3.353**	**0.000**
	Negative	**21**	**78.05**	**7.652**	**1.670**	

EEG WITH PHES -MHE:

EEG		PHES POSITIVE	PHES NEGATIVE	TOTAL
SUGGESTIVE	COUNT	3	0	3
	%WITHIN EEG POSITIVE	100%	0%	100%
	%WITHIN PHES POSITIVE	15.8%	0%	7.5%
NOT SUGGESTIVE	COUNT	16	21	37
	%WITHIN EEG POSITIVE	43.2%	56.8%	100%
	%WITHIN PHES POSITIVE	84.2%	100%	92.5%
TOTAL	COUNT	19	21	40
	%WITHIN EEG POSITIVE	47.5%	52.5%	100%
	%WITHIN PHES POSITIVE	100%	100%	100%

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.585(b)	1	.058		
Continuity Correction(a)	1.670	1	.196		
Likelihood Ratio	4.737	1	.030		
Fisher's Exact Test				.098	.098
Linear-by-Linear Association	3.495	1	.062		
N of Valid Cases	40				


PHES
40
35
30
25
20
15
10
5
0
16
21
37
3
0
3
PHES POSITIVE
PHES NEGATIVE
TOTAL INDIVIDUALS
EEG SUGGESTIVE
EEG NOT SUGGESTIVE

RESULTS

- In our study mean age of controls is 45.3,mean age of cases is 45.28.from 20 to 30 years no controls ,2 cases present,from 31 to 40 -12 subjects were controls,8 patients were cases,from 41 to 50 years 16 were controls,19 were cases.from 51 to 60 years 12 were controls,11 were cases.p value was 0.987,so age wise no significant difference present.
- In our study in controls 32 males and 8 females were present,in cases 31 males and 9 females were present.p value is 0.785.so statistically not significant.
- In NCT-A 21 cases were PHES positive, 19 were PHES negative.the mean value in controls were 65.63 and in cases were 77.28.
- In NCT-B 26 cases were PHES positive,14 were PHES negative.the mean value in controls was 91.80 and in cases was 115.05.
- In DST 40 CASES WERE PHES positive,no cases were PHES negative.the mean value in controls is 24.65,in cases were 17.83.

- In LDT 27cases were PHES positive,13 cases were PHES negative.the mean value in controls was 64.03 and in cases were 76.83.
- In CDT 24 cases were PHES positive and 16 cases were PHES negative. The mean value in controls 66.47 and in cases was 79.83.
- From this PHES is positive in 19 cases and in 2 controls .PHES negative in 21 cases and 38 controls.p value is <0.001.so MHE is present in 19 cases [47.5%] out of 40.
- Out of these 19 cases ascites was detected in 11 cases.so chances of MHE is more common in decompensated liver disease.
- Out of the 40 cases bilirubin was more than 5.405 and ammonia was more than 93 microgram/dl in 19 cases and bilirubin was less than 2.681 in 21 cases. ammonia was less than 78 micrograms/dl in 21 cases.
- Out of these 19 cases EEG changes was observed in only 3 cases, so EEG does not help to detect patients with MHE.it can be used as follow up tool.

DISCUSSION

DISCUSSION

Number of patients taken up for study:

Study groups	total number of controls, cases
Seo YS et al	200 160
Su Wen li et al	146 53
Present study	40 40

AGE:

The mean age of controls and cases are

Seo YS et al	41+13, 55+8
Su Wen li et al	37.3+10.5, 45.6+8.2
Present study	45.30, 45.28.

The mean age of controls was higher than previous studies and the mean age of cases was parallel to previous studies.

SEX DISTRIBUTION :

The sex distribution in the studies are

Seo YS et al 100 [50%] men were controls, 102[63.8%] men were cases,

Su Wen li et al 99 [67.8%] men were controls, 50[94.3%] men were cases,

Present study 32[80.0%] men were controls, 31[77.5%] men were cases.

PHES SCORE:

By applying PHES score, MHE was diagnosed in

41 patients [25.6%] by Seo YS et al

26 patients [49.1%] by Su Wen li et al

19 patients [47.5%] In present study.

CORRELATION WITH SEVERITY OF LIVER DISEASE:

In the study by Su Wen li et al, cases with child Pugh B, C had a higher proportion of PHES positivity, MHE. In the present study cases with ascites had a higher proportion of PHES positivity.so PHES correlates

well with decompensated liver disease. And decompensated liver disease patients are more prone for MHE.

CORRELATION WITH SERUM AMMONIA:

In the study done by Su Wen li et al serum ammonia was done in 26 cirrhotic patients and was found to be similar between MHE and non MHE groups.in the study done by Roxana et al, serum ammonia level increased significantly in cirrhotic patients after oral glutamine compared to control group.In the present study serum ammonia level is increased in 19 cases.

So from the present study, PHES score is statistically significant in detecting MHE in cirrhotic patients. Patients with severe liver disease with ascites, increased ammonia had high PHES positivity.

CORRELATION WITH EEG :

In our stud EEG changes were seen in only 3 patients with PHES positive, so EEG is not effective in detecting MHE.EEG can be used for follow up of patients with hepatic encephalopathy.

CONCLUSION

CONCLUSION

- PHES score is statistically significant in detecting minimal hepatic encephalopathy in cirrhotic patients.
- Incidence of MHE is more with severe liver dysfunction.

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BIBLIOGRAPHY:

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ANNEXURES

“PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR THE DETECTION OF MINIMAL HEPATIC ENCEPHALOPATHY IN SOUTH INDIAN PATIENTS WITH LIVER CIRRHOSIS”

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY :

TREATMENT HISTORY :

GENERAL EXAMINATION :

VITALS :

SYSTEMIC EXAMINATION

CENTRAL NERVOUS SYSTEM:

ABDOMEN :

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM :

LIVER FUNCTION TESTS:

ULTRASONOGRAM OF ABDOMEN:

PHES:

SERUM AMMONIA:

EEG:

INFORMATION SHEET

We are conducting a study on **"PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR THE DETECTION OF MINIMAL HEPATIC ENCEPHALOPATHY IN SOUTH INDIAN PATIENTS WITH LIVER CIRRHOSIS"** among patients attending Rajiv Gandhi Government General Hospital, Chennai.

The purpose of this study is to standardize the PHES in healthy south Indian population and evaluate the prevalence of MHE among south Indian patients with liver cirrhosis

In this study we will be performing number connection test, A, B, Line drawing test, Digit symbol test, Circle dot test. For this test we will be providing paper and pen. This test is done to assess the motor speed, accuracy, concentration, attention and memory.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator	Place : Signature of Participant
Date :	

<u>ஆராய்ச்சி தகவல் தாள்</u>

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனைக்கு வரும் நோயாளிகளின் கல்லீரல் சுருங்கிய நிலையில் வரும் தென்னிந்திய நோயாளிகளுக்கு ஏற்படும் வெளிப்படையாக தெரியாத ஆரம்பகால மூளை பாதிப்பு நோயினை PHES **மூலம் கண்டறிதல் பற்றிய ஆராய்ச்சி நடைபெறுகிறது.**

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். PHES செய்முறை மூலம் நோயாளிகளை ஆராய்ச்சி செய்து அதன் மூலம் கிடைக்கும் மதிப்பீடுகளை ஆராய்வோம்.

இந்த ஆராய்ச்சியில் number connection test, A, B, Line drawing test, Digit symbol test, Circle dot test கொடுக்கப்படும். உங்களுக்கு பேனாவும், பேப்பரும் கொடுக்கப்படும். இந்த பயிற்சி மூலம் உங்களின் புத்திக் கூர்மை, வேகத் தன்மை மற்றும் ஞாபக சக்தி கண்டறியப்படும்.

இந்த ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியின் முடிவுகளை ஆராய்ச்சின் போது அல்லது ஆராய்ச்சின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இவ்வாய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. G. Kumaravel
Postgraduate MD (General Medicine),
Madras Medical College,
Chennai – 600 003.

Dear Dr. G. Kumaravel,

The Institutional Ethics Committee has considered your request and approved your study titled **Psychometric Hepatic encephalopathy score for the detection of minimal Hepatic encephalopathy in Cirrhotic patients in South Indian Population No.05082014.**

The following members of Ethics Committee were present in the meeting held on 03.06.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.S.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandhini, M.D., Inst.of Pharmacology, MMC	: Member
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9. Prof.Tito, M.D., Director i/c, Inst.of Internal Medicine, MMC.	: Member
10.Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MASTER CHART

“PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE FOR THE DETECTION OF MINIMAL HEPATIC ENCEPHALOPATHY IN SOUTH INDIAN PATIENTS WITH LIVER CIRRHOSIS”

MASTER CHART

Controls

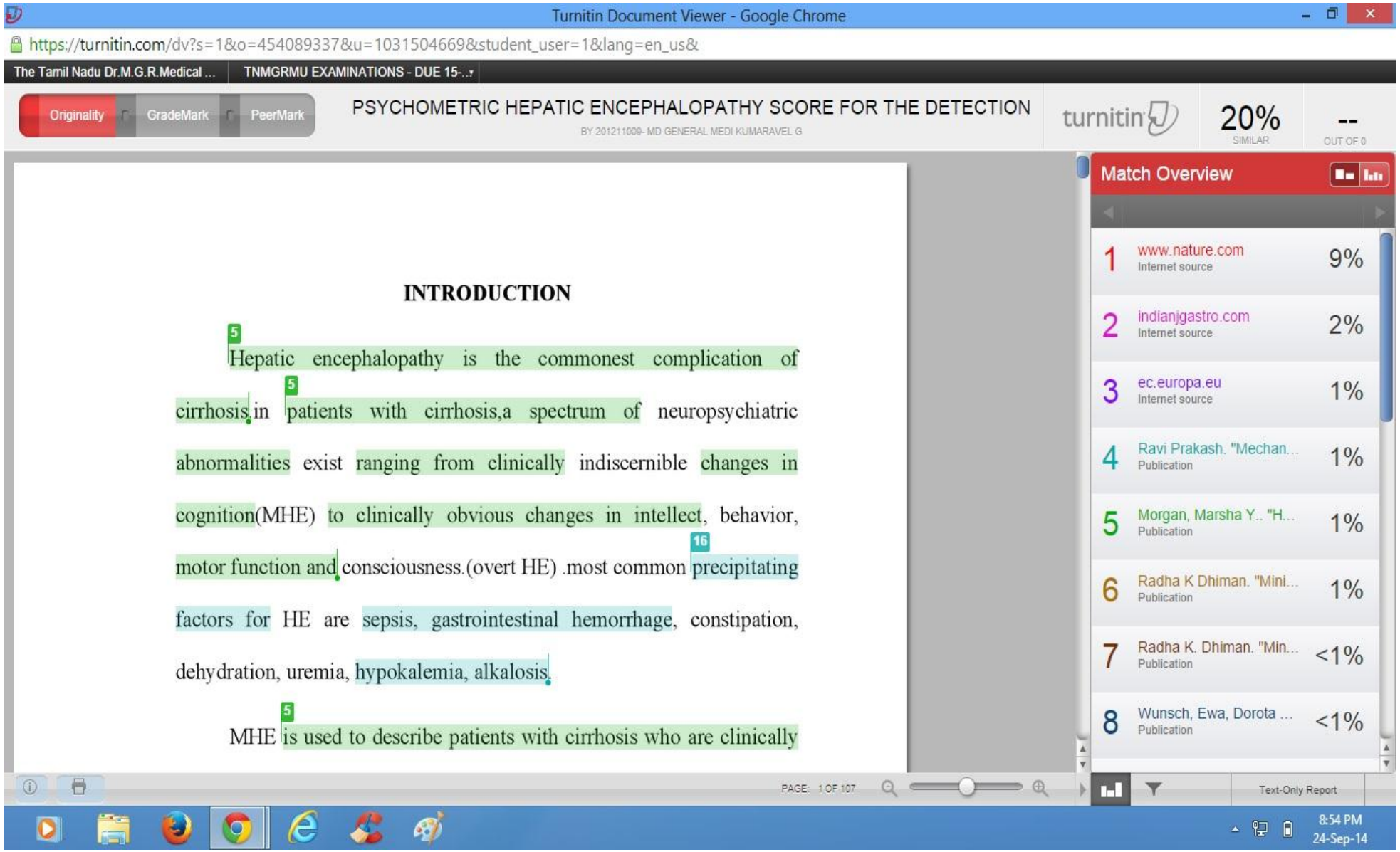
S.NO	AGE	SEX	NCT-A (sec)	NCT-B (sec)	DST (box)	LDT (sec)	CDT (sec)
1	41	M	66	102	27	54	50
2	58	M	74	80	32	62	66
3	47	M	42	92	26	42	74
4	52	M	76	100	36	76	73
5	55	F	53	96	22	53	60
6	49	M	44	104	24	49	69
7	38	M	62	86	32	62	42
8	56	M	66	93	20	66	72
9	39	F	78	120	22	78	69
10	44	F	72	76	28	72	55
11	48	M	69	88	24	66	68
12	52	M	70	104	26	69	63
13	46	M	63	110	22	63	75
14	36	M	66	92	24	70	66
15	42	F	73	78	20	66	72
16	57	M	76	86	19	73	54
17	41	M	71	84	24	76	56
18	52	M	68	96	26	71	69
19	46	M	64	104	22	68	44
20	38	M	74	102	29	64	73
21	35	M	76	86	19	74	76

22	53	M	73	88	20	76	74
23	44	F	69	92	22	73	79
24	41	M	44	96	19	69	68
25	56	M	56	76	26	47	65
26	51	M	59	82	25	56	74
27	38	M	72	86	22	47	76
28	48	M	66	92	23	56	65
29	36	M	63	101	19	44	68
30	39	M	65	88	24	72	72
31	45	F	73	86	30	66	63
32	52	M	68	94	32	63	70
33	37	M	55	76	25	65	69
34	48	M	69	82	19	73	72
35	38	F	72	90	30	68	78
36	47	M	43	110	32	55	66
37	52	M	60	89	19	69	62
38	37	M	69	104	24	72	54
39	36	F	72	76	26	43	76
40	42	M	74	85	25	73	62

MASTER CHART - CASES:

S.NO	AGE	SEX	NCT-A (sec)	NCT-B (sec)	DST (box)	LDT (sec)	CDT (sec)	USG (ASCITES)	TOTAL BILIRUBIN mg/dL	AMMONIA µgm/dL	EEG
1	53	M	68	110	22	56	88	no evidence	2.4	74	not suggestive
2	45	M	94	103	11	62	76	no evidence	3.6	72	not suggestive
3	56	F	56	142	14	68	102	present	8.6	104	not suggestive
4	38	M	62	88	18	66	98	no evidence	2.5	83	not suggestive
5	43	M	72	102	14	68	76	no evidence	2.6	81	not suggestive
6	48	M	102	152	12	93	88	present	5.6	98	suggestive
7	52	M	56	110	12	74	112	present	4.6	96	not suggestive
8	38	F	68	98	32	68	84	no evidence	3.6	68	not suggestive
9	42	F	90	86	24	72	86	no evidence	2.8	72	not suggestive
10	55	M	96	153	10	106	88	present	7.2	107	not suggestive
11	36	M	76	96	28	84	76	no evidence	2.6	81	not suggestive
12	28	M	98	166	10	88	74	present	12.8	93	not suggestive
13	45	M	65	149	22	96	57	no evidence	3.6	69	not suggestive
14	38	F	56	98	24	66	68	no evidence	3.9	74	not suggestive
15	47	M	98	164	8	92	68	no evidence	10.7	118	not suggestive
16	49	M	112	163	20	72	72	present	8.8	93	suggestive
17	52	M	72	172	13	112	98	present	6.9	116	not suggestive
18	35	M	68	98	16	98	103	no evidence	3.5	99	not suggestive
19	46	M	66	84	14	68	72	no evidence	2.8	84	not suggestive
20	48	M	96	162	11	88	74	present	6.8	95	not suggestive
21	44	M	88	98	16	56	62	present	3.2	93	not suggestive
22	49	M	84	88	11	64	99	no evidence	2.5	83	not suggestive
23	37	F	102	162	19	86	86	present	4.8	106	not suggestive
24	52	F	72	152	22	76	72	no evidence	1.9	73	not suggestive
25	56	M	76	78	21	98	66	no evidence	1.6	75	not suggestive
26	55	M	64	86	23	67	68	no evidence	2.4	81	not suggestive

27	43	M	68	94	24	49	68	no evidence	2.6	67	not suggestive
28	46	M	98	173	12	103	92	present	5.9	96	not suggestive
29	38	M	76	112	26	92	104	no evidence	1.8	72	not suggestive
30	56	M	88	148	12	72	124	present	4.2	103	not suggestive
31	43	M	76	98	19	67	86	no evidence	1.8	81	not suggestive
32	48	M	72	87	13	63	72	no evidence	2.8	73	not suggestive
33	38	F	66	76	22	82	68	no evidence	2.2	76	not suggestive
34	51	M	68	66	19	76	62	no evidence	1.8	82	not suggestive
35	49	M	92	182	10	74	89	present	2.8	96	suggestive
36	28	M	86	66	23	83	68	no evidence	1.7	86	not suggestive
37	43	M	56	82	24	88	56	no evidence	2.5	73	not suggestive
38	46	F	58	98	19	59	72	no evidence	2.4	76	not suggestive
39	51	F	62	62	22	62	57	no evidence	2.4	77	not suggestive
40	44	M	68	98	21	59	62	no evidence	1.8	69	not suggestive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INTRODUCTION
Hepatic encephalopathy is the commonest complication of cirrhosis.in patients with cirrhosis,a spectrum of neuropsychiatric abnormalities exist ranging from clinically indiscernible changes in cognition(MHE) to clinically obvious changes in intellect, behavior, motor function and consciousness.(overt HE) .most common precipitating factors for HE are sepsis, gastrointestinal hemorrhage, constipation, dehydration, uremia, hypokalemia, alkalosis.
MHE is used to describe patients with cirrhosis who are clinically
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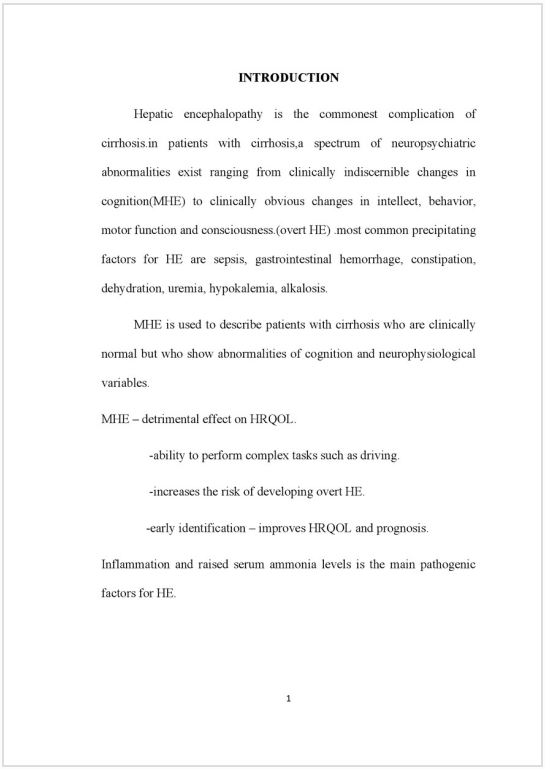

INTRODUCTION

Hepatic encephalopathy is the commonest complication of cirrhosis.in patients with cirrhosis,a spectrum of neuropsychiatric abnormalities exist ranging from clinically indiscernible changes in cognition(MHE) to clinically obvious changes in intellect, behavior, motor function and consciousness.(overt HE) .most common precipitating factors for HE are sepsis, gastrointestinal hemorrhage, constipation, dehydration, uremia, hypokalemia, alkalosis.

MHE is used to describe patients with cirrhosis who are clinically normal but who show abnormalities of cognition and neurophysiological variables.

MHE – detrimental effect on HRQOL.

-ability to perform complex tasks such as driving.

-increases the risk of developing overt HE.

-early identification – improves HRQOL and prognosis.

Inflammation and raised serum ammonia levels is the main pathogenic factors for HE.

1