SERUM ZINC LEVELS IN DECOMPENSATED LIVER DISEASE AND ITS CORRELATION WITH THE STAGE OF HEPATIC ENCEPALOPATHY

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations For the award of the degree of

M.D. GENERAL MEDICINE (BRANCH - I)
INSTITUTE OF INTERNAL MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

APRIL 2015

CERTIFICATE

This is to certify that the dissertation titled **"SERUM ZINC LEVELS IN DECOMPENSATED LIVER DISEASE AND ITS CORRELATION WITH HEPATIC ENCEPALOPATHY"** is the bonafide original work of Dr.Rajesh Kumar Meena in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in September 2014. The Period of study was from April 2014 to September 2014.

Prof.S.Tito, M.D.,
Director & Professor of Medicine
Madras Medical College &
Rajiv Gandhi Government
General Hospital
Chennai 600 003

Prof.Rajasekaran, M.D.,
Prfessor of Medicine
Madras Medical College &
Rajiv Gandhi Government
General Hospital
Chennai 600 003

Dr.Vimala, M.D.,
Dean
Madras Medical College &
Rajiv Gandhi Government General Hospital
Chennai 600 003

DECLARATION

I, Dr. RAJESH KUMAR MEENA solemnly declare that dissertation titled "SERUM ZINC LEVELS IN DECOMPESATED LIVER DISEASE AND ITS CORRELATION WITH THE STAGE OF HEPATIC ENCEPALOPATHY" is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during April 2014 to September 2014 under the guidance and supervision of my unit chief PROF. S. RAJASEKARAN, M.D., Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in General Medicine – September 2014.

Dr.Rajesh Kumar Meena
Final Year Postgraduate,
Department of General Medicine,
Madras Medical College,
Chennai - 600 003.

Place: Chennai
Date:

ACKNOWLEDGEMENT

I owe my thanks to Dean, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3. **Prof.Vimala, M.D.,** for allowing me to avail the facilities needed for my dissertation work.

I am grateful to beloved mentor **Prof.S.Tito, M.D**., Director and Professor, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-03 for permitting me to do the study and for his encouragement.

With extreme gratitude, I express my indebtedness to my beloved Chief and teacher **Prof.S.Rajasekaran, M.D.,** for his motivation, advice and valuable criticism, which enabled me to complete this work.

I am extremely thank full to **Prof.Narayanaswamy, M.D,** H.O.D and Professor of Hepatology for allowing me to avail the facilities and guiding me through the study.

I am extremely thankful to my Assistant Professors **Dr.Thangam, M.D., Dr.Azhagu Thyagarajan, M.D. Dr.Damodaran, M.D.** and **Dr.Jeyakumar, M.D.** for their guidance and encouragement.

I am also thankful to all my unit colleagues **Dr.Karthik, Dr.Sudha Mallika, Dr.Yusuf, and Dr.Vivekananand** A for their full cooperation in this study and my sincere thanks to all the patients and their families who co-operated for this study.

Finally I thank my parents and all my family members who gave me their full support and co-operation in completing the dissertation.

ABBREVIATIONS

ALD	Alcohol liver disease
BCAA	Branched Chain Amino Acid
DCLD	Decompensate Chronic Liver Disease
DTR	Deep Tendon Reflex
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HE	Hepatic Encephalopathy
GIT	Gastro intestinal tract
MHE	Minimal Hepatic encephalopathy
NT	Neurotransmitter
PHT	Portal Hypertension
TIPS	Trans jugular Intrahepatic Porto-systemic Shunt
GABA	Gamma Amino Butyric Acid
TNF	Tumour Necrosis Factor
TGF	Tumour Growth Factor
5-HT	5-Hydroxy Tryptophan
UGI	Upper Intestinal Bleed
TB	Total Bilirubin
AST	Aspartate Transaminase
ALT	Alanine Transaminase
NK	Natural killer cells
H.pylori	Helicobacter pylori
HBsAg	Hepatitis B surface antibody

KF Ring	Kayser Fleischer Ring
PT	Prothrombin Time
INR	International Normalized Ratio
GABA	Gamma Amino Butyric Acid
WHC	West Haven classification
EEG	Electroencephalography
PHES	Psychometric hepatic encephalopathy score
NCT	Number connection test
SBP	Spontaneous bacterial peritonitis
EVL	Endoscopic variceal ligation

CONTENTS

SERUM ZINC LEVEL IN DECOMPENSATED LIVER DISEASE AND ITS CORRELATION WITH STAGE OF HEPATIC ENCEPALOPATHY

Rajesh Kumar Meena[1], Rajasekaran S[2]

OBJECTIVE /AIM:

The purpose of this study to assess serum Zinc levels in DCLD patients with various stage of hepatic encephalopathy and determine the role of Zinc deficiency in precipitation of hepatic encephalopathy.

MATERIAL AND METHODS:

The descriptive cross sectional study was conducted at Rajiv Gandhi Government General Hospital and Madras Medical College Chennai

Total 75 cases, all patients above 20 year of age, both sex and diagnosed cases of DCLD, admitted in hepatic encephalopathy. All cases were further evaluated for serum Zinc and all patients were divided according to stage of hepatic encephalopathy and class of liver cirrhosis. The data was analyzed with statically soft ware (SPSS) and the p-value <0.001 was considered as statically significant.

RESULT:

In our study showed 96% male and 4% female, predominantly affected group between 30-50 year of age (63%). Most common aetiology was alcohol abuse (90%), more than 10 year duration. All DCLD patients in HE had low serum Zinc, low serum Zinc significantly associated with worse grade of HE and advanced class of liver cirrhosis (p-value 0.001). Our study also shown those patients have low serum albumin significantly associated with low serum Zinc (p-value 0.029)

CONCLUSION:

The inferences attained from the study are all patients in DCLD with hepatic encephalopathy identified low serum Zinc. More drops in serum Zinc is correlated with worse grade of HE, low serum Zn indirect precipitating factor of HE. Low Zn level also associated with higher class of cirrhosis and low albumin Short term Zn supplementation may be useful in prevention and treatment in HE patients.

Key Words:

Decompensate Chronic Liver Disease (DCLD)

Hepatic encephalopathy (HE)

Serum Zinc

Albumin

INTRODUCTION

Liver disease affects millions of people worldwide every day. In developing countries like India, cost of health care has always been an issue.

Chronic disease like liver cirrhosis and its complication are a major health problem, in India ,where large population are living with poverty, poor hygienic environment , lack of education . Burden of cirrhosis patients is keep on increasing; most of the patients are admitted in hospital with complication of cirrhosis.

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation. It is the end result of the fibro genesis that occurs with chronic liver injury [1]

Diffuse fibrosis cause architecture distortion with regenerative nodule formation results in decreased liver cell mass and reduced blood flow to the liver.[1,2]

In India most common cause of cirrhosis is alcohol abuse and viral hepatitis. Reversible fibrosis with ongoing injury in course of time develop a decompensate condition (DCLD) that associated one or more complication like ascites, jaundice, Hepatic encephalopathy& UGI bleed.

Hepatic encephalopathy (HE) a life threatening complication that can be occur in acute or chronic liver failure .About 30% patient of cirrhosis die due to hepatic coma .[5]HE in patient of liver failure is an indication of poor prognosis, in a cirrhotic patient HE develop due to one or more precipitating factor or due to fulminate liver failure or it could be a result of prolonged portal systemic shunting .

Hepatic encephalopathy probably due to gut derived neurotoxin such as ammonia. Other key factors are astrocytes dysfunction, disturbed neurotransmitter regulation and oxidative stress developed in astrocytes.

Zinc is an essential trace element ,second most abundant trace element in the body .Zn is associated with more than 300 enzymatic system [7] It is an important co –factor in urea cycle, have a great role in conversation of ammonia to urea .Zn increase the natural defense of reactive oxygen radical, Zn also act as an antioxidant ,anti apoptotic agent ,co- factor for DNA synthesis and an anti inflammatory agent .So deficient Zn levels seems to have effect in pathogenesis of Hepatic encephalopathy.

AIM AND OBJECTIVES OF STUDY

Aim of this study observe serum zinc level in DCLD patient with various stages of hepatic encephalopathy and determine the role of zinc deficiency in precipitation HE .Study will also describe association of zinc deficiency according child's Pugh class, level of albumin and anorexia, malnutrition, vomiting, diarrhea, age, duration of alcohol intake in DCLD patient.

REVEIW OF LITERTURE

GENERAL CONSIDERATION

Cirrhosis is defined as anatomically as a diffuse process with fibrosis and nodule formation, due to various etiology.[1,14] Cirrhosis is dispersed septal fibrosis of the liver, associated with regenerative parenchymal nodules formation and forms fibrous sheets which are links portal tracts and central zones. Cirrhosis results from prolonged and hepato-cellular necrosis due to various reasons[14].

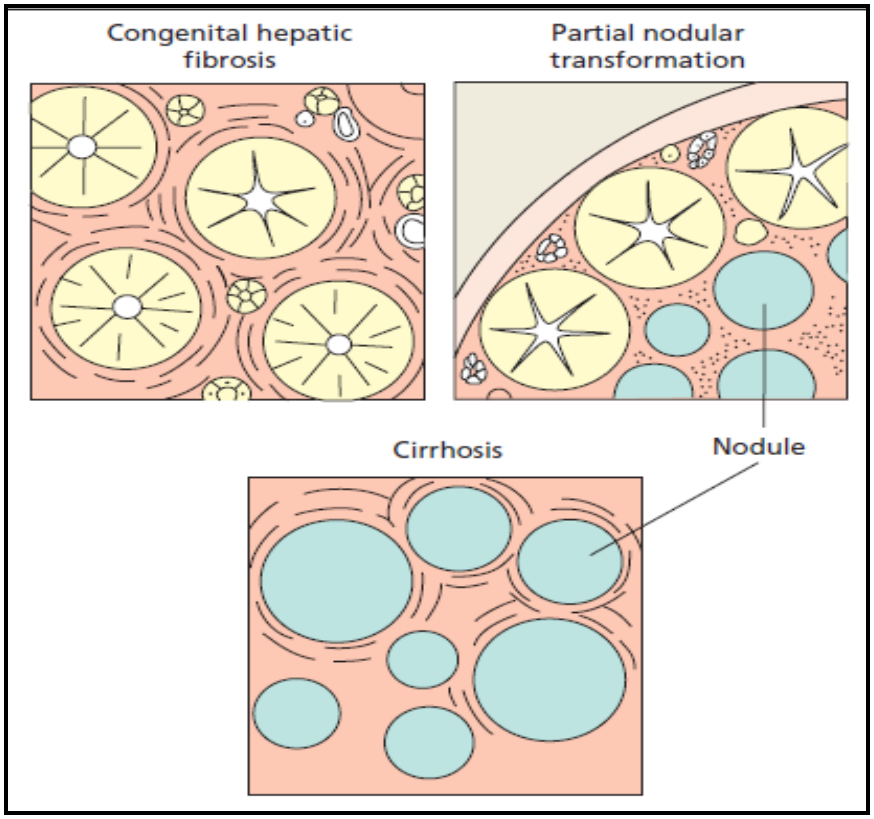

Figure1- Cirrhosis-fibrosis with nodules formation

These diseases should be detected as early as possible, fibrosis alone cannot say cirrhosis, and Formation of nodule in absence of fibrosis as in partial transformation is not cirrhosis.

CAUSE OF CIRRHOSIS[1, 2]

1) Alcohol abuse

2) Chronic viral hepatitis (B,C and D)

3) NSAH (Non alcoholic steatohepatitis)

4) Metabolic causes;

   a. Copper over load (Wilson disease)

   b. Type 4 glycogenesis

   c. α 1 antitrypsin deficiency

   d. Iron over load (Haemochromatosis)

   e. Galactosaemia

   f. Cystic fibrosis

   g. Glycogen storage disease

5) Biliary Tract Disease

   a. Extra hepatic biliary obstruction

b. Intra hepatic biliary obstruction

c. Primary biliary cirrhosis

6) Auto immune hepatitis

7) Primary Sclerosing cholangitis

8) Hepatic venous out flow block – Heart failure

Budd –chiari syndrome

9) Toxin and drug e.g.; Methotrexate,amiodrone

In developing world main cause is viral hepatitis, but alcohol and autoimmune condition may be increasing.

In western countries alcoholic abuse most common cause of DCLD but NASH (Non alcoholic cirrhosis) and viral cirrhosis (particular hepatitis C) are increasing.

EPIDEMIOLOGY

Chronic liver disease and cirrhosis causes 30000-450000 deaths each year in India.

Many patient die from the disease in the fourth to fifth decade of the life. Most of death due to complication of DCLD, Each year

additional 4000 deaths are attributed to Acute Fulminate Liver Failure (FLF).

FLF may be caused by viral hepatitis (B, C&E), Drugs and Toxin induced (e.g. acetaminophen, cabon tetrachloride, Amanitaphalloid), Auto immune hepatitis, Wilson's disease etc, [9] patient with FLF have 50-80% mortality rate. One third patient of FLF due to unknown etiology

ETIOLOGY IN INDIA[9,10]

Common cause of cirrhosis in India

- Alcoholic Liver Disease (35%)
- Post infectious causes (30%)
- Unknown causes (18%)
- Post Hepatic & Biliary causes (8%)
- Miscellaneous (9%)

Risk factor associated with cirrhosis also depend on[11]

1) Age
2) Sex
3) Duration of disease

4) Diabetic mellitus

5) Poor immunological status

6) Life style

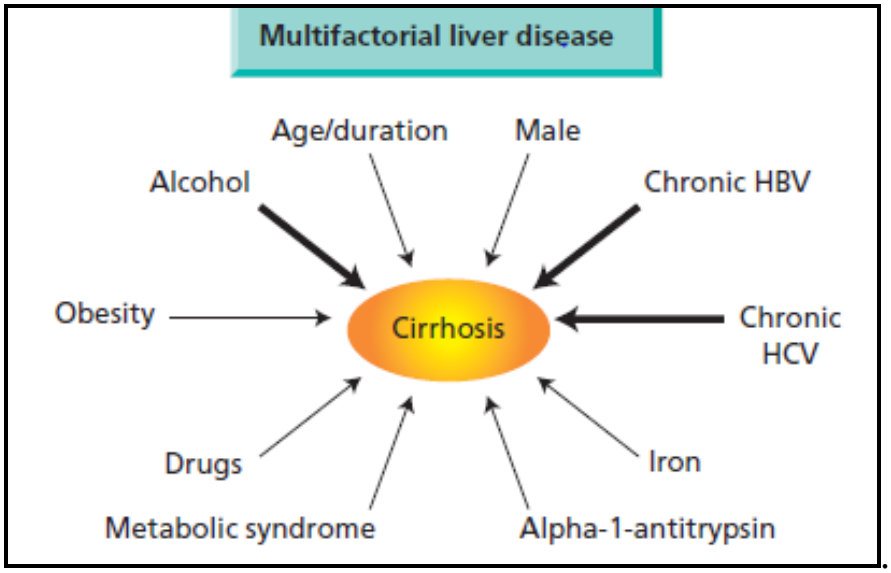

Figure2- Major Risk for cirrhosis

The terms compensate and decompensate generally used for cirrhosis. Some words about terms-

COMPENSATED CIRRHOSIS[16, 18]

Compensated cirrhosis can be symptomatic or asymptomatic. Mostly without any sign and symptom of liver failure, patient diagnose during routine screening or at operation time. Liver injury

on going in this stage but it is reversible in nature, due to response of liver injury healing process will start known as fibrogenesis.

It started by activation of stellate cell due to secretion of cytokines, fibrosis may be progress and can become irreversible if not treat it at time[16].in this stage firm hepatomegaly and mild spleen may present, some sign like ankle swelling, vascular spider palmer erythema can be occur, liver function may be quite within normal range in this group, most of time mildly elevation in serum transaminase or gamma –glutamyl transpeptidase concentration, confirmation of cirrhosis by liver biopsy and liver imaging , liver biopsy confirmatory gold standard test,[14,15] compensated phase can be precipitate by excessive alcohol intake, drugs , infection and trauma, mild portal hyper tension may present in this stage without liver function abnormality , We can treat patient successfully and completely by removing causative agent and liver protective medication, by early diagnosis and by measuring the viral load we can control HBV and HCV induced liver cirrhosis also.

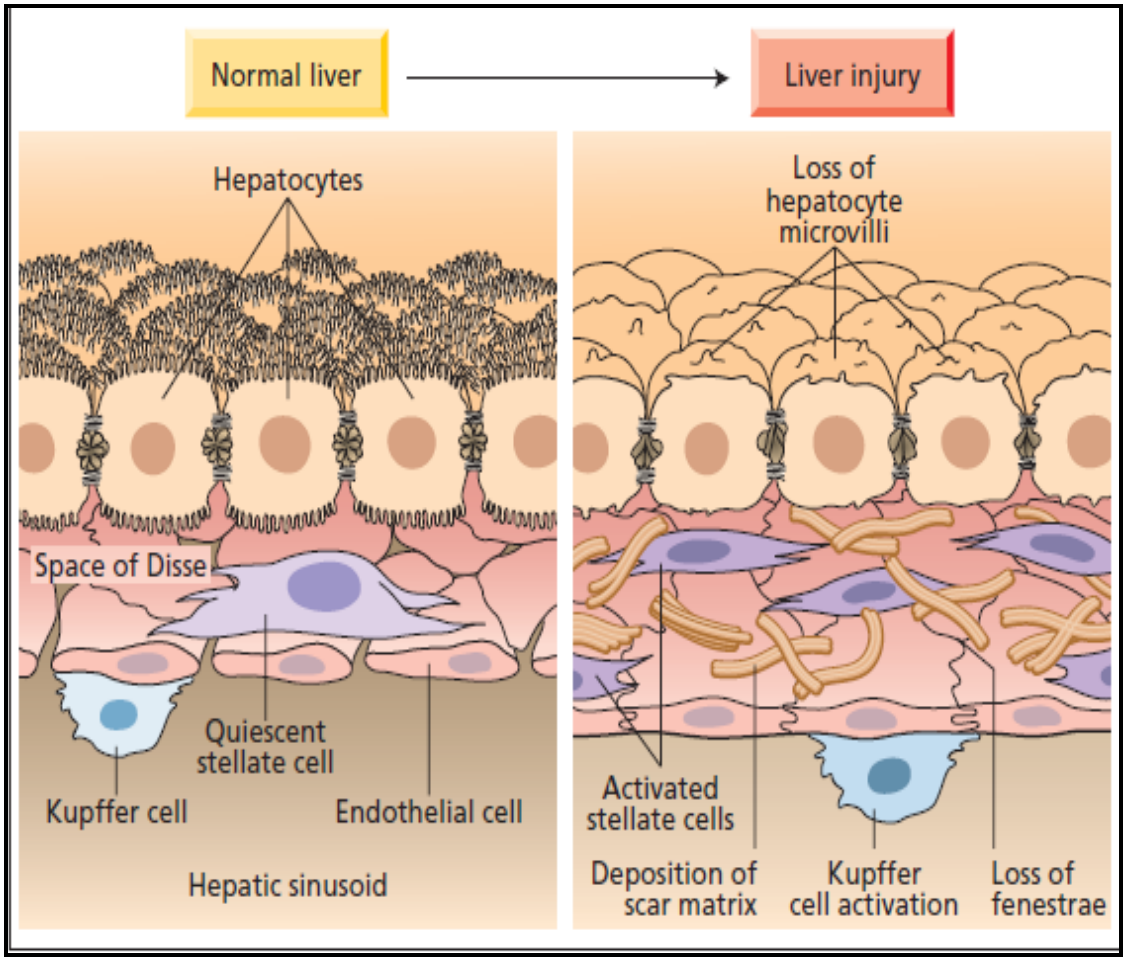

Figure: 3- Cellular and matrix change after chronic liver injury

DECOMPENSATED CIRRHOSIS[1, 24];

Ongoing liver injury and fibro genesis in decompensate stage patient develop bridging fibrosis and nodules formation.

Fibrosis can be centrilobular ,periportal or pericellular, After a advanced fibrosis liver architecture disruption may occur, development of portal hypertension most common complication of decompensation, appears in form of ascites as a first sign of decompensation.

The patient in this condition need hospitalization due to complication of progressive cirrhosis like ascites, jaundice ,or gastrointestinal bleeding and other serious complications of liver failure, like hepatic encephalopathy ,hepatorenal syndrome ,hyponatremia and spontaneous bacterial peritonitis. General health poor with weakness, muscle wasting and weight loss.

Continuous low grade fever (37.5 -38^{0}c) caused by gram negative bactraemia, continuous ongoing hepatitis lead to liver necrosis.

Ongoing alcoholic hepatitis leads to end stage as hepatocellular carcinoma. Jaundice indicate that active liver cell destruction more than the regeneration capacity, severity of jaundice is always alarming sign, severe jaundice indicate more loss of liver function and acute liver failure in chronic cirrhosis.

Other manifestations like skin pigmentation, clubbing, purpura may associated with decrease platelets counts, patients may have hypotension loss body hair, vascular spiders, Erythema on hands, dupuytrens contracture, discoloration of nails and genital atrophy, enlargement of parotid glands and gyanecomastia are

common in DCLD. Pallor due to UGI bleeding, flapping tremor in HE.

The liver may be enlarged, if enlarged than smooth surface, firm and regular edge in initial stage but in advanced CLD liver usually shrunken and impalpable. The spleen commonly palpable may be moderate to severe enlarged, most of complication due to hyper dynamic flow of blood and vasodilation[21] Cirrhosis broadly divided in alcoholic cirrhosis, chronic viral cirrhosis due to hepatitis B and C, biliary cirrhosis and others.

PATHOPHYSIOLOGY OF CIRRHOSIS

The liver cirrhosis occurs due to change in the normally well maintain processes of extracellular matrix formation and degradation. The usual scaffolding for liver cells are formed by of collagens (type I,II III, V,) proteoglycans , glycoprotein and matrix cellular protein .All component of extracellur matrix maintain the function of hepatocytes, Stellate cells, situated in the peri-sinusoidal have important role for formation of extracellular matrix.

Stellate cells (Ito cells) may become activated after chronic liver injury. Activation of stellate cell occur in two phase ,first

initial phase occur due to paracine stimuli and prolongation stage due to paracrine and autocrine stimulation during perpetuation stage of stellate cell many change occur in cell behavior lead to proliferation, secretion chemotaxic agent, fibro genesis, contractility of hepatic cell.

ECM degradation, inflammatory and immune response, by the initiation of these stellate cell change into collagen producing cells by various paracrine factors released by hepatocytes and kupper cells. Like TGFβ1, MMP-2, MCP-1, PGDF and ET

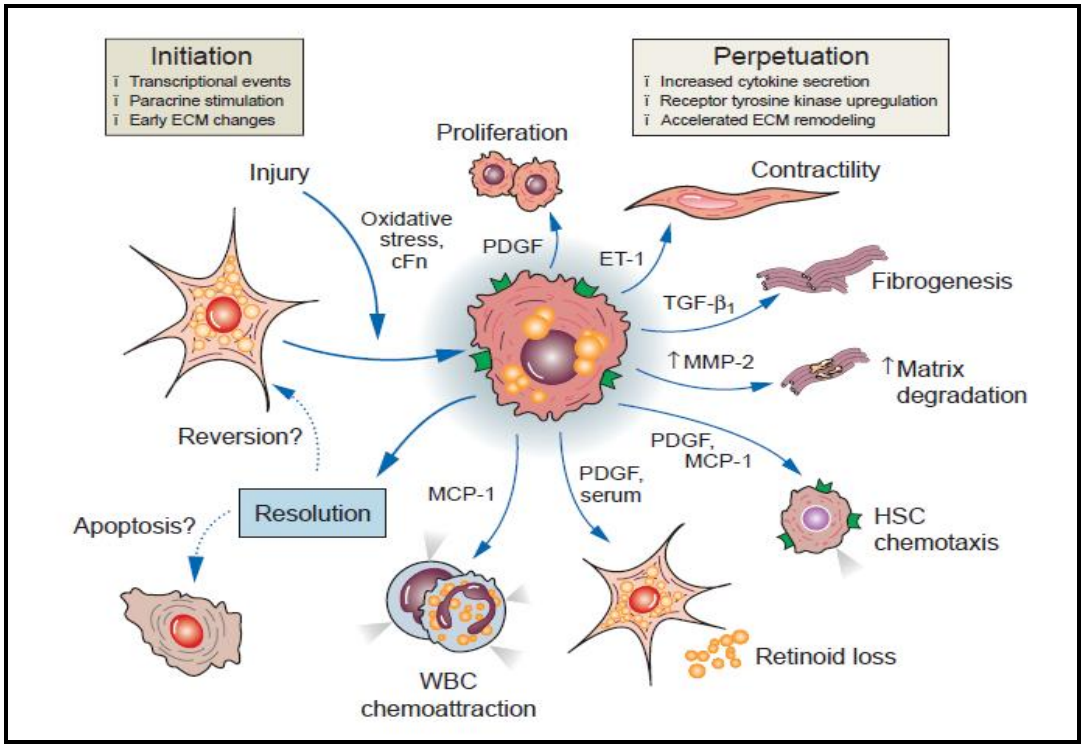

Figure: 4 -Liver stellate cell activation due to response of liver injury

The mediators after these effect shown various change in behavior of stellate cell , platelets and sinusoidal endothelium cell after chronic liver injury e.g. Increased cytokines(TGFβ1) transforming growth factor β 1 is found in patients with chronic hepatitis C and Cirrhosis.[22] TGF β 1 release activate stellate cells to produce type 1 collagen formation , that excessive collagen deposition in the space of Disse and the decreased size of endothelial fenestrate that increase the Capillarisation of sinusoids. Activated stellate cells also have contractile properties. Both capillarisation and constriction of the sinusoids cell due to the stellate cells lead to the development of portal hypertension. In future, treatment to prevent fibrosis should focus on decreasing hepatic inflammation, avoid the activation of stellate cells, blocking the fibrogenic agent and fibrogenic activity of stellate cell.[30,31]

HISTOPATHOLOGY:

The typical histological feature of cirrhosis is diffuse liver fibrosis and regenerative hepatic nodules formation.

With micro nodular cirrhosis the nodules are uniformly small and similar in size to liver lobules.

In macro-nodular cirrhosis the nodules are hetrogenous in size and may be more than10mm.

It may not be visible on needle biopsy as complete nodule formation. Other features like fragmentation and pattern of fibrosis on reticular staining suggest the proper diagnosis.

Cell necrosis is the evidence of active regeneration and cellular infiltrate shows etiological agent is still survives in liver cell and destruction is ongoing.

Whenever we are taking the biopsy from the histological specimen, the biopsy should be from the nodules. Open biopsy in Laparoscopic examination gives good results

Endoscopic guided biopsy is also a good option for histological diagnosis but that is under development phase.

Biopsy very useful in undiagnosed etiology of cirrhosis[14, 15]

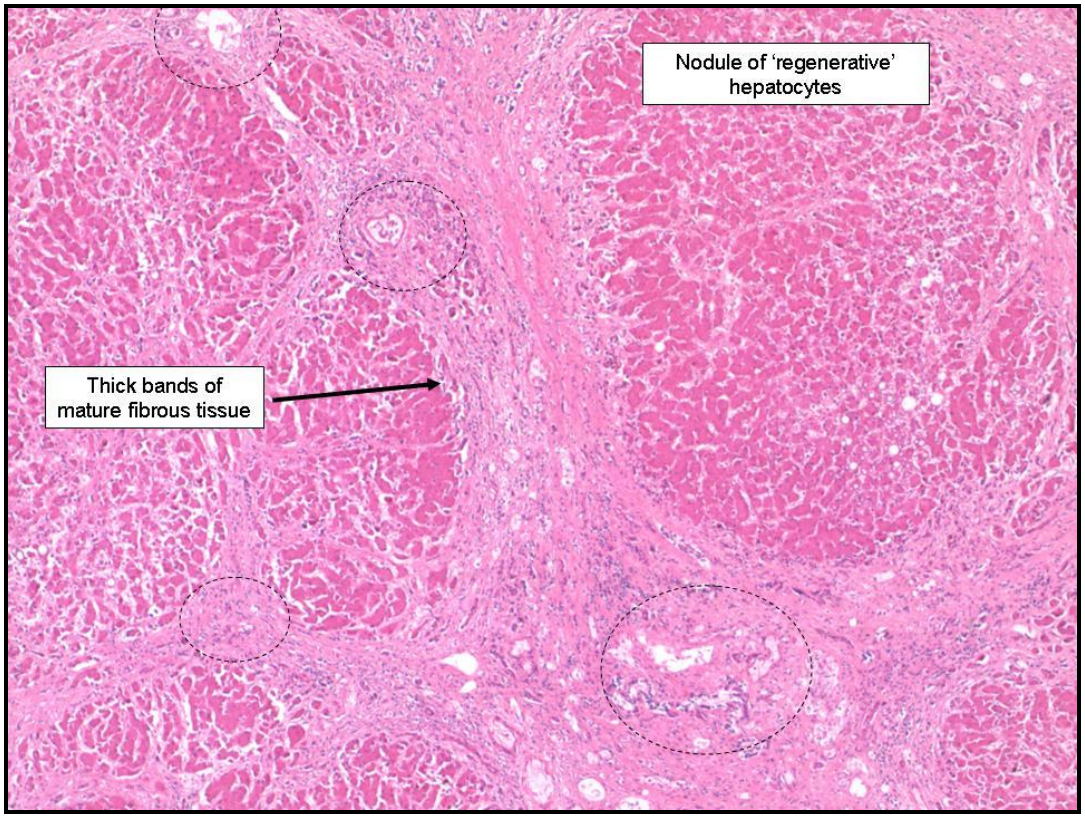

Figure : 5- Histopathology of cirrhosis of liver showing fibrosis and nodules of regenration in hepatocytes

CLINICAL FEATURES

Many cases cirrhosis may be incidentally found without symptoms or signs during at routine examination. An evidence of the presence of cirrhosis and its etiology usually comes after complete history.

SYMPTOMS

- Jaundice is can be absent in cirrhosis. If jaundice present that suggests either the causative agent is still active, that ongoing injury is reason for decompensation, or a drug toxicity might

have caused further impairment liver function that cause elevation of bilirubin levels[1,2].

- Easy fatigue ability, tiredness, weakness or breathing difficulty are common and contributes to the poor general health in cirrhosis patients. Anorexia present commonly occur cases of cirrhosis, When present it is an alarming sign of liver failure. Weight loss is seen in end stage liver disease[37].

- Nausea and Vomiting are very common. A remediable cause should be come first. Vomiting may be in form of upper UGI bleeding, content should be examined to rule out haematemesis.

- Abdominal pain or discomfort is common, pain present in the right upper quadrant or right lower ribs. Ill-defined vague pain and generalized abdomen discomfort due to distention caused by ascites

- Constipation or loose stools, both may occur in cirrhotic patient, both can be precipitate the complication of cirrhosis.

- Abdominal hernia occur with ascites ,water and salt retention leads volume overload state can occur as edema of ankles and legs.

- Pruritis is an important diagnostic clue for primary biliary cirrhosis.

- Difficulty in breathing may be associated with massive ascites. In Some patient of cirrhosis, dyspnoea may be associated with fibrosing alveolitis, pulmonary shunting, pulmonary hypertension and Hepatic-pulmonary syndrome[39,40]

- Patient of liver cirrhosis develop spontaneous bleeding from the gums or nose. UGI bleeding present in form of hemetemesis and malena. Coagulopathy can be occur severe liver failure.

- Neurological complication of DCLD like hepatic encephalopathy. Due to failure of urea cycle in liver lead to increase ammonia level affect the brain. HE also sign of fulminate hepatic failure, most common cause to hospitalization of cirrhotic patient, Depression is common.

- Fever can present as a symptom spontaneous bacterial peritonitis common may have no obvious cause.

PHYSICAL SIGNS

- Most patients with cirrhosis look poor built, with the late stage liver disease, muscle wasting and loss of adipose tissue commonly from face and neck occur bone may become prominent known as cirrhotic faces[38].

- An acute worsening of nutritional appearance may suggest infection or bleeding, while more prolonged deterioration results from liver decompensation. Anemia due to bleeding from UGI tract or iron deficiency due to prolonged loss of blood. Jaundice suggests liver decompensation and usually an alarming sign of fulminate liver failure in CLD patient.

- Cyanosis is uncommon except there is marked pulmonary shunting. Mild shunting is common in cirrhotic. Hypertrophic ostoearthropathy may also be present.

- Skin changes like Spider naevi, Paper money skin[43], erythema of palm etc are present in cirrhosis more commonly in alcoholic cirrhosis. Excessive bruising noted when hepatic function deteriorates severely.

- DCLD patients especially those with hemochromatosis show of hyper pigmentation with widespread melanin pigmentation.

Vitiligo appears in autoimmune liver disease. Lichen planus is associated with primary biliary cirrhosis.

- Testicular atrophy is common in DCLD mainly in alcoholic Cirrhosis or hemochromatosis, Gynaecomatia seen in patient who taking spironolactone, patient usually presented with loss of pubic and axillary hairs and signs of feminization. Manse disturbance common in female44,45,

- Dupuytren's contracture and Parotid enlargement are more common in alcoholic cirrhosis. They are sign related to alcoholism more than to cirrhosis. Kayser- Fleischer ring is a particular sign to look for in the case of Wilson's disease as it is a potentially treatable cause.

ABDOMINAL SIGN

Abdomen maybe distended due to accumulation of fluid or rarely due to enlargement of abdominal organs. Skin over distended abdomen may appear dry and rough with prominent veins. Multiple dilated veins can be seen. Ascites most is common in DCLD.

The abdomen appears distended and flanks are full and the umbilicus is out ward and everted. Shifting dullness may present. Dilated veins may be seen all over the abdominal wall peri-

umbilical known as caput medusa or dilated vein over the flanks indication of Budd -Chiari syndrome.

Enlarged liver or spleen can increase local bulging of the abdomen, a firm cirrhotic liver may be normal or mild enlargement, significantly palpable in the early stages, shrunken liver in late stages with nodularity.

Measurement of the liver span is helpful in diagnosis of shrunken liver.

The normal range is 12-16 cm. (average 14 cm); a contracted liver is easily picked up by USG. Abdomen percussion is helpful in diagnosis of ascites Auscultation may useful for clinical diagnosis of a Liver bruit for large hepatoma or a venous hum indicates portal Hypertension. A friction rub over the hepatic area indicate hepatocellular carcinoma. A continuous venous hum heard over the epigastrium known as Baumgartner sign.

In enlarged veins the direction of flow should be determined. The Presence of the veins and their position should be marked.

The presence / absence of lower leg swelling are also very important differential clue in between occlusive disease of veins and Budd Chiari syndrome.

INVESTIGATION

Total Blood Count

Routine hematological values can be normal in all cirrhotic patients.

Low hemoglobin is common. Normocytic normochromic anemia on blood films target cells may be seen and in acanthocytes may see rarely in alcoholic cirrhosis and other features of haemolysis may be seen. The White Cell count tends to low in cirrhosis patient due to hypersplenism.

If white cell count is raised an indication of infection should be take seriously. The platelet count is usually low in the cirrhotic due to hypersplenism. Liver cell injury decrease production of Coagulation factor in liver, coagulation factors usually low in advanced liver cirrhosis. Vitamin k depended factors 2, 7, 9, 10 are commonly affected. Factor VII is the most affected and earliest changes also occur in factor 7concentration in cirrhosis.

Prothrombin time is prolonged in decompensated cirrhotic

BIOCHEMICAL TESTS

Liver Function Test

Liver function test limited role in cirrhosis, as it may be normal. AST and ALT can be normal or high in cirrhosis if causative factor is no longer active and enzymes can come to normal with effective therapy,(like Interferon, Ribavarine). In alcoholic cirrhosis liver enzymes usually elevated, AST/ALT ratio is usually greater than 2.

In most patients's serum alkaline phosphatase usually elevated about two times to normal except in biliary cirrhosis there level more raised. The gamma glutamyl transferase and serum transaminase level elevated in alcoholic cirrhosis.[51, 52] The serum total bilirubin level is can be normal in early stage of cirrhosis . But in decompensation stage bilirubin will be increased, other cause of increased bilirubin load in DCLD patient due to haemolysis, UGI bleed, and certain drugs like steroids. A raised in bilirubin without any obvious cause suggest hepatic decompensation.

Low serum protein and serum albumin levels are usually present in DCLD, synthesis of albumin reduced in cirrhosis patient. However hypoalbuminea also due to extracellular fluid volume

expansion or due to gastric causes (poor intake, malnutrition) or renal pathology also can associate with low albumin level.

RENAL FUNCTION TEST

Plasma electrolytes disturbance usually associated with cirrhosis and patient need close monitoring. Hyponatremia is most common usually due to reduction of free water solute clearance and total body water intake, hyponatremia may be due to salt loss due to diuretic therapy it is important risk factor for hepatic encephalopathy[47]. Hypernatremia is less common in cirrhosis patient and may occur with GI bleed, excessive use of lactulose and with severe fluid restriction. Serum potassium is usually normal in cirrhotic patients. But both hyper and hypokalemia can occur depending upon the type of diuretic use for treatment E.g.spironolactone produces hyperkalemia, while loop diuretics like furesemide produces hypokalemia. Urine sodium and potassium monitoring are useful to decide diuretic therapy. Spironolectone serious side effect is hyperkalemia, we can increase the dose of spironolactone till the urine sodium/potassium ratio is more than one. Hypomagnesaemia and Hypophosphatemia are also common occur in alcoholic patient with cirrhosis. The electrolyte abnormality can precipitate DCLD complication should be

diagnosed and treated as early as possible. In well compensated cirrhosis, the urea level is normal but it may be low or high once decompensation occurs due to disturbance in urea cycle in liver. So renal failure in cirrhosis should be monitors by serum creatinine. Renal failure in cirrhosis patient is common due to diuretics over use, hypotension hepatorenal syndrome etc. Fasting blood glucose is usually low.

But most of the cirrhosis are insulin resistant and have post prandial hyperglycemia .The serum cholesterol free triglyceride level increase in cirrhotic patient.

SERUM MICRO ELEMENTS LEVEL IN DCLD PATIENT;

Patient with advanced cirrhosis serum zinc level usually low. Low level in DCLD associated hypoproteinemea, and also due to use of diuretic that cause excessive discharge from urine, that level more low HE.

Malnutrition and poor oral intake may also relate to zinc low level. Zinc have important co-factor of urea cycle enzymes .that can lead to failure urea cycle as the result this blood ammonia level will be increase, that is a important pathogenesis of HE in cirrhotic patient . Zn level more low with increase stage of hepatic

encephalopathy .manganese level usually high in DCLD patient .both Mn and Zn are have important role in DCLD related complication.

ANATOMICAL AND PATHOLOGICAL DIAGNOSIS

The diagnosis of cirrhosis depends on demonstrating widespread fibrosis in the liver combined with nodules.

THIS MAY BE DIAGNOSED BY

1) **Laparoscopy:** direct visualizes the liver and enables direct biopsy.

2) **Ultrasound abdomen:** is suggested by dense reflective areas of irregular distribution and increased echogenicity. Shrunken liver and spleenomegaly commonly occur in DCLC. However ultrasound is not reliable for diagnosis unless ascites is present.

3) **CT scan**: Liver size can better assessed and usually irregular nodular surface seen. Hepatic and portal vessels can be imagined with contrast. Ascites can be seen and gall stone can be visualized.

4) **Liver Biopsy:** Reticular and collagen stains are need to highlight the fibrosis. Liver cell size in variable size and shape in cirrhosis and presence of nodules with fibrous septa important clue in diagnosis.

5) **Radioiso top scaning;** in experimental phase.

INVESTIGATION FOR ETIOLOGICAL DIAGNOSIS

It is important to establish the causative agent of cirrhosis. The following investigation may be useful

1) Serology of viral hepatitis:

- ❖ HBsAg
- ❖ IgM and IgG anti HBV Antibody
- ❖ IgM AND IgG anti HCV antibody
- ❖ HCV RNA titer
- ❖ Liver biopsy
- ❖ Hepatitis B Viral load

2) Serum Iron and Hepatic Iron content to rule out hemochromatosis.

3) Eye examination for KF ring by slit lamp and serum ceruloplasmin and serum and urinary copper to rule out Wilson's disease

4) Anti Smooth Muscle Antibody

5) Anti LKM Antibody

6) Anti-mitochondrial Antibody

7) Serum α – Fetoprotein to rule out hepatocellular malignancy

COMPLICATION OF DCLD

Major complications

1) ***Portal Hypertension-*** This is the major complication of cirrhosis but these can be occur due to by extra hepatic portal vein thrombosis or Non cirrhotic portal fibrosis.

2) ***Ascites-*** Abdominal distension also very common presentation of DCLD

3) ***Hepatic Encephalopathy-*** Major Cause of sensorial disturbance and unconsciousness in DCLD patients. Encephalopathy can be caused by other metabolic process also should be rule out in DCLD.

4) ***Hepatocellular carcinoma-*** Serious complication of cirrhosis with very poor prognosis

5) ***Infection-*** Spontaneous bacterial peritonitis an important cause for sudden deterioration of cirrhosis patient, occur with low grade fiver and abdominal pain. Most common due to gram negative bacteria.

UGI BLEEDING

Associated with portal hypertension and peptic ulcer disease in alcohol cirrhosis, may occur due to varices develop in esophagus and hemorrhoids.

OTHER COMPLICATIONS

1) Anemia & Haemolysis
2) Fluid electrolyte disturbance
3) Hepatopulmonary Syndrome
4) Hepatorenal Syndrome
5) Hepatopulmonary Syndrome
6) Gallstones

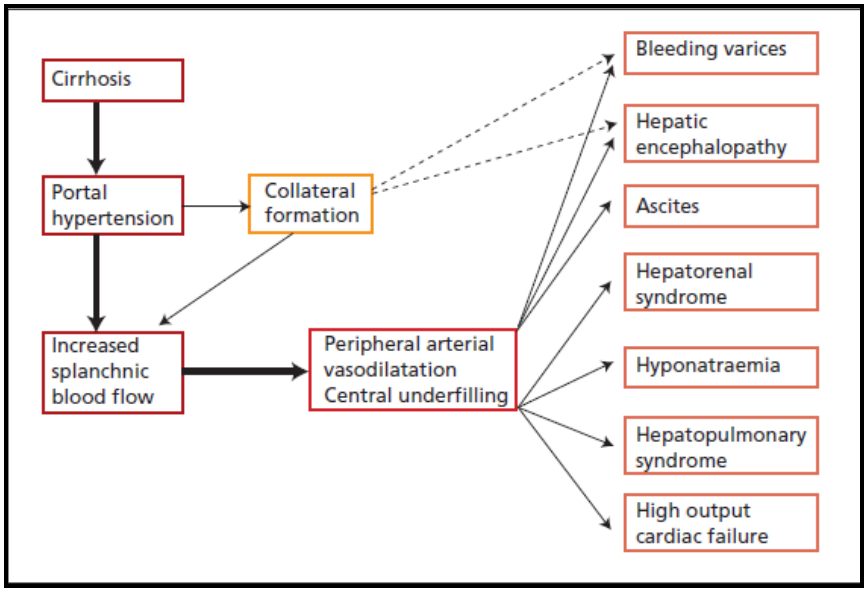

Figure: 6- Complication in cirrhosis patient due to hyper dynamic circulation

PROGNOSTIC INDICATORS

Child –Trucot Pugh score[58,59];

Table1- Child-Pugh classification

Clinical Variable	1 point	2 point	3 point
Encephalopathy	None	Stage 1-2	Stage 3-4
Bilirubin(mg/dl)	<2	2-3	> 3
Albumin(G/dl)	>3.5	2.8-3.5	> 2.8
Prothrombin Time prolonged in sec or INR	<4 sec or INR <1.7	4 sec or INR 1.7-2.3	>6 sec or INR >2.3
Ascites	None	slight	moderate to severe

Class A score=5-6, Class B score=7-9, Class C score=10-15

2. MELD SCORE[60][Model for end stage liver disease];

It was develop for need of TIPS in cirrhotic patient, depend on

1) Serum Bilirubin

2) Serum Creatinine

3) Prothrombin time(INR)

Important use of MELD score for liver transplant listing and short out for Priority of liver transplant

Cox Regression Model

Poor prognosis is associated with:

- ❖ Marked Ascites
- ❖ Prolonged PT and elevated INR
- ❖ Gastrointestinal Bleeding
- ❖ Old Age
- ❖ High Serum Bilirubin
- ❖ Continuing Alcohol Consumption
- ❖ Spontaneous Bacterial Peritonitis
- ❖ Neurological complication

- Etiology
- Liver size; enlarged liver good prognostic sign
- Portal venous pressure persistent low blood pressure (systolic BP less than 100mmhg)

TREATMENT:

The management of reversible fatty liver is focused towards early pick up of liver fibrosis. An adequate balanced diet and abstinence from alcohol are essential. A balanced diet of 1-1.5 g of Protein per kg of body weight is adequate. Liver- protectives are not very much helpful.

DCLD patients with volume overloaded state like edema and ascites should be treated with

1) low salt diet
2) Fluid restriction.
3) Diuretics.

Specific treatments to prevent complication like lactulose for soft and free stool to prevent hepatic encephalopathy, treatment for portal hypertension, gut stabilizer like Rifaxamine or neomycin, GI

bleeding prevention) should be instituted. Use of antibiotic needed if there is evidence of infection e.g. fever, abdominal pain, monitoring and treatment of electrolytes abnormality required, vitamin K useful in DCLD.

ANTIFIBROTIC THERAPY

1) **Colchicine**: Microtubule inhibitor, it's a relative less side effect drug, only complication being diarrhea, and some efficacy in preventing progression of Cirrhosis.

2) **Steroids**: Useful in autoimmune hepatitis, if DF more than 32 indication of steroid use if there is no contraindication of steroid. Otherwise has no role in therapeutics of alcohol cirrhosis.

3) **Interferon**: Efficacy not proven in ALD. Useful in case of chronic viral hepatitis

SERUM ZINC LEVEL IN DCLD PATIENT.[61, 62, 64]

Zinc is an important trace element that required essentially for body growth and development, also has important role in activation of many enzymes, Zinc is a co-factor for these enzymes. Zn level in DCLD patient usually low .possible causes of zinc deficiency in DCLD. Due to poor intake of Zn, malnutrition, low

protein diet, excessive loss of Zn through GI tract. Mostly zinc in body present bound form ,it may loosely bound with albumin and tightly associated with α2-globulin ,significantly Albumin level low in DCLD patient[4] , patients who have more low serum albumin concentration also prone for more zinc deficiency ,low albumin level is one of most important cause of zinc low level in DCLD , other cause of low zinc level in DCLD patient are loss of appetite ,patient of DCLD .patient of cirrhosis usually have anorexia and malnutrition due to poor dietary intake also one reason of low Zn , Available Zn also not useful due to lack of albumin. Diuretics are important part of treatment of DCLD patient, The excess use of diuretic also increase the urinary secretion of Zn. frequent bowel wash and lactulose also increase GI loss of zinc ,low zinc level affects more than 300 enzymatic system of body ,Zn is important co-factor for urea cycle enzymes and has great role in conversion of ammonia to urea ,due to deficiency of zinc urea affect the brain that can cause neurological disturbance in DCLD patient[69,70] ,That called as hepatic encephalopathy , patient those has HE also has more low serum zinc , Zn deficiency one of precipitating factor for HE .

Due to Zn low concentration many skin manifestations also occur in DCLD patient may has growth retardation and hypogonadism. Loss of immunity also can occurs due to zinc deficiency that all are associated with poor prognosis,

ZINC

Zinc is an essential trace element and plays an important role not only in catalytic reaction but also in the maintenance of structural integrity of protein by forming zinc finger like structure created by chelation centre including cysteine and histidine residues and regulation of gene expression.

ZINC STRUCTURE

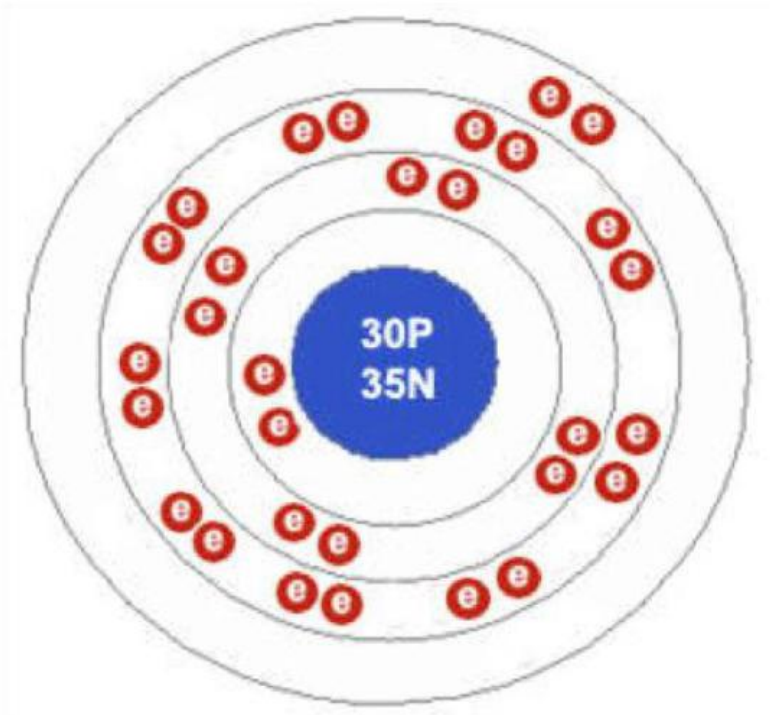

Figure: 7- Zinc structure

HISTORY [72]

Zinc was found metallic form zinc ore were used for making brass and zinc compounds were used for healing wound and eye sores first isolated pure zinc discovered by Andreas Sigsimund Marggarf.

Brass a zinc alloy was produced by the romans in the time of Augustus [20BC -14AD] Charaka Samhita thought to have been written in 500BC or before mention which oxidized, The produces pushpanjan zinc mines at Zawar near Udaipur in India have been active since Mauryan period The smelting of metallic zinc here to have begun around the 12^{th} century AD Biological role of zinc was recognized by Raulin in 1869 2a ,He observed that zinc was required for aspergillus niger growth , In 1934 zinc role in rat as essential element proved,

Chemistry [73]- Zinc second most abundant micro element in body, Zn [atomic weight -65.39 and atomic no-30] lies at end of first transition series ZN^{+2} a stable ion with complete 3D electron shell, zinc is excellent electron acceptor with no redox reaction, has fast legend exchange kinetics and flexible Co- ordination *geometry* One hypothesis says that zinc ions present in cytoplasm at 10-

11mol/L and Zn also present in metelloenzymes and transcription factor[74]

Dietary sources[75] – Zinc is a widely distributed in non vegetarian diet, mainly protein bound form, the most available source are red meat and fish .

For vegetarians bean and wheat germ are good source but Zn content can be reduced by milling and food processing,

Distribution[77] – an adult weighing 70kg has 1.4 to 2.3 gm zinc in body it is distributes various parts of body in following order;

1) Skin and prostate;70-80mg /100gm (Highest)

2) In kidney, liver, muscles, heart ,pancreas and spleen ; 2.3to5.5mg/100gm

3) Brain and lung;1.4to1.5mg/100gm

ZN absorption, metabolism and excretion – Daily intake of zinc 12 gm/day in normal adult ,about 20% part of total intake absorption by GI tract but low intake condition absorption can be increase up to 100%, these measurement made by stable Zn tracer to assess Zn homeostasis and plasma Zn kinetic.

Estimation of Zn absorption has also been compared by using different isotope techniques, the absorption of zinc from diet is inhibited by dietary phytate, fiber, oxalate copper and iron; some drug also reduced Zn absorption,

The absorbed zinc come to the liver by portal circulation where active integration into metalloenzyme and plasma protein as albumin andα2microglobin.

Blood plasma has less than 1%of the total body zinc and present in marrow concentration 80-120 micro/dl ~80% of plasma zinc bound with albumin and rest Zn tightly bound with α2 macroglobulin.

Zinc in plasma in poise with plasma aminoacid [histidine and cysteine] and that small ultra filterable percentage may important in cellular in take mechanism,

Total body zinc at least 1.4 -2.3 gm , it is present in the cell of all active tissue organ, about ~55% in muscle, 30 in prostate, semen ,and retina and bone ,RBC(red blood cell) Zn present in form carbonic anhydrase , so Zn in RBC 10% high compare to plasma , Fecal excretes both unabsorbed dietary Zn and remove from gut , total excretion about 10-15 mg/dl, o.5% Zn remove by urine, zinc

excretion increase during catabolic illness and also increase in starvation , as a result remove from skeleton muscle and excretion of Kenton bodies[78]

Requirement ; Zn for normal health has been recommended 0.2 mg Zn per kg body weight , Adult man and woman need 15 to 20 mg day , during pregnancy and lactation require 25mg Zn daily.

Function of zn[73,77] ;

More than 300 Zn contained metalloenzyme in all six categories of enzyme system, as example Alkaline phoshatase , carbonic anhydrase, RNA and DNA polymerases, carboxypeptidase and alcohol dehydrogenase.

The important role of zinc protein and nucleic acid synthesis , explain the failure of growth and wound healing observed in individual with Zn deficiency ,Protein can from domain which bind with tetrahedral zinc atom by co-ordination with histidine and cystein and form a folded structure that known as ‘ Zinc Finger’ ,which is a biologically active units have main role in gene expression by acting as DNA –binding transcriptor factor and play key role in development biology and Zn also regulate steroid , thyroid and other hormone synthesis

Zinc bind with metal response factor MTF-1 and actives metalloprotein [Mt] expression , that multifunction low molecular weight protein has high cystein which reversible bind zinc ,MTF-1 is important intracellular Zn trafficking and help to balance intracellular Zn concentration ,Storage and secretion of insulin; Secretary vesicles of pancreatic beta cell which stored insulin as crystalloid like hexamers , each stable by binding with Zinc to thiol or imidazole side chain amino acid of insulin ,Elimination of free radical ; as a co-factor of superoxide dismutase(cytoplasmic). Zn plays main role removal oxide free radical by SDM[79]

Role in Alzheimer disease-Both Zn deficiency and toxicity precipitated Alzheimer disease, excess Zn bind to peptidase site of amyloid

Taste sensation- Zn protein gluten has role gustatory function[80]

Role in vita A metabolism ; Zn has role to stimulate the release of vitamin A from hepatic cell to blood and increase vita A in plasma , also its utilization in rhodopsin synthesis, Role in growth and development; Zinc deficiency lead to hypogonadism and dwarfism , Zn concentration notice less in plasma RBC ,urine

and stool in such patient's deficiency decrease spermatogenesis in male and menstrual cycle are disturbed in female Zn deficiency due to phyrate rich diet can cause poor body growth , failure of puberty and hypogonadism in human,

Role in wound healing;

Zinc high concentration has been found in granulation tissue in and around the healing wound,

Role in biosynthesis of mononucleotide-

The synthesis of mononucleotide and their integration in to nucleic acid has been found to be impaired in Zn deficiency,

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a serious and common complication of liver disease, potentially reversible, or progressive complication associated neurological and psychological disturbance of brain function, known as a brain functions alteration neuropsychiatric syndrome.[1,2]

It is characterized by brain functions alteration lead to cognitive dysfunction, behavior abnormality and changes in personality transient neurological symptoms and characteristic EEG (electroencephalographic) low frequency with high amplitude patterns can be present with acute and chronic liver failure. Hepatic encephalopathy is associated with severe liver insufficiency ,The characteristic manifestations are wide range of neurological and psychiatric symptoms loss of orientation ,loss of working memory(WM), visuospatial disturbance , changes in personality as irritability ,lack of interest , emotion disturbance , decrease physical activity , abnormal sleep cycle pattern ,day time sleeping observed ,motor system like decrease tone increase deep tendon reflex , bilateral planter extensor , flapping tremor may occur advanced stages of HE, the development of acute encephalopathy with an progressive sudden worsening in the level of consciousness, presented as severe confusion

,stupor or coma.[85,86] Usually some precipitating factor are identified with acute encephalopathy, for treatment of the episode is directed towards the removal of the precipitating cause . Once the causative factors are treated successfully the encephalopathy disappears, patient recover to previous state. However, if patients with end stage liver disease has less reserves of liver function the hepatic encephalopathy may be a persistent condition. The low hepatic function reserve causes spontaneous chronic HE. those patient have multiple portal-systemic anastomosis ,therapeutically created TIPS also important cause of persistent HE There is mostly a precipitating factor for HE , such patient present with episodic HE, once precipitating factor like dehydration ,UGI bleeding, constipation occur patient redevelop hepatic and brain dysfunction and the diagnosis and treatment should base on such aspects related to precipitant. Chronic hepatic encephalopathy may be manifest as recurrent episodes of acute encephalopathy known as chronic-episodic encephalopathy or associated with persistent neurological disturbance may be prominence of neurological manifestations. In clinical practice, distinction is difficult because acute episodes occur with the chronic-persistent encephalopathy. The difference between the two forms is subjective and is reflected in the chronic presentations, if the manifestations are mild, we can use term “recurrent encephalopathy”. On

the other aspect, if the manifestations are chronic and severe, the term "persistent encephalopathy" should be used. In patients who present with chronic recurrent HE, episodes can be associated with a precipitant factor but generally are spontaneous or related to the end stage of treatment. It is frequently occur that these episodes are attributed due to constipation. An episode acute on chronic in encephalopathy usually occur has an abrupt onset and recovered fast with termination of precipitating factors. Between episodes, the patient may be conscious and alert and not any signs of cognitive function loss, unless he or she is examined for minor hepatic encephalopathy by construction aprexia or neuropsychological Testing.

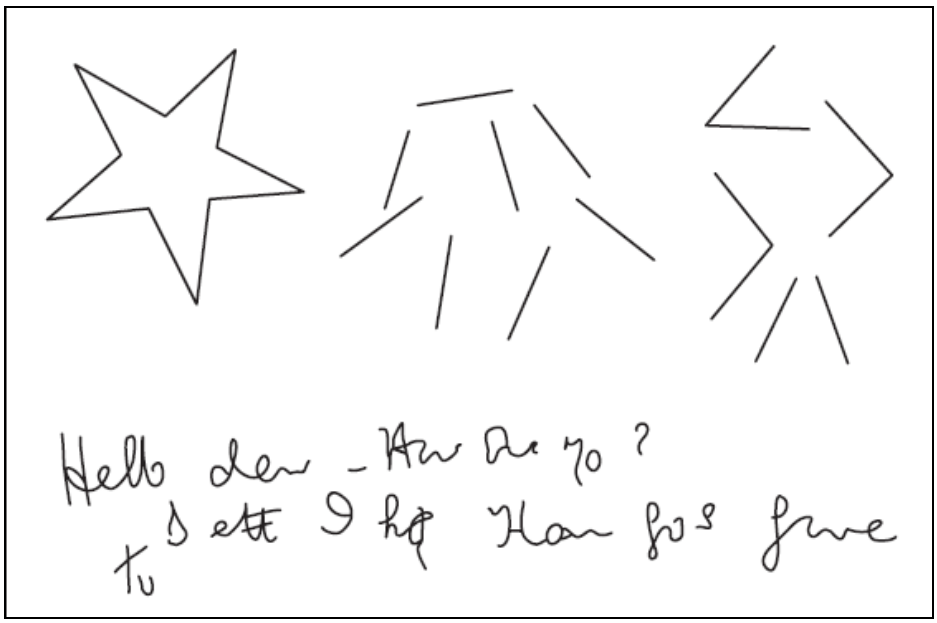

Figure: 8- patient with minimal hepatic encephalopathy unable to copy above star and figures, difficulty in writing also present. [1]

Pyramidal and /or extra pyramidal signs may present with persistent encephalopathy, seizure uncommonly reported with HE

PATHOGENESIS OF HE; [1,96,97,98,100,101]

For many years, controversy about the pathology is there about the production of the toxic substances which is causative for the altered cerebral state. There has been always consideration about the role of ammonia, GABA , synergic toxins or endogenous benzodiazepines in the development of hepatic encephalopathy. There are peripheral multi-systemic dysfunctions, and changes in the intercellular transmission in brain, produced by changes in astrocytes. Key role in pathogenesis in HE are neurotoxin produced by gut, dysfunction of astrocytes, brain water homeostasis, disturbance of neurotransmitters, oxidative stress and inflammation in brain and infection

PERIPHERAL SYSTEMS

1. Intestinal

There is debate for the role of *H. pylori*, ammonium produces by these bacteria in the GIT, ammonia has key role in the development of HE. Some studies trial demonstrated a high prevalence of the infection H.pylori in patient with alcoholic hepatitis, as well as individuals with cirrhosis and chronic HE.

But it seems role of micro organisms in the development of HE may be low.

2. Liver failure:

Hepatic failure is one of the important cause for the development of hepatic encephalopathy, resulting from reduced liver functional activity that reduces the clearance of ammonium, high blood levels of ammonium is responsible for clinical manifestations HE.

3. Portal-systemic shunting:

Congenital portal-systemic shunts in children, presented with hepatic encephalopathy, even without hepatic disease. Also, patient of DCLD with portal-systemic shunts prone for HE.

4. Muscle:

Poor muscle mass and loss nutritional status in DCLD patients prone for the complication like HE. Muscle wasting associated with increase of TNF-α, which stimulates transcription factors e.g. NK-a, resulting in decreased synthesis of myosin protein. Poor muscle mass reduces capacity of muscle in detoxification of glutamine and ammonium, resulting that patient can present with high ammonia level lead to hepatic encephalopathy.

BRAIN ALTERATIONS:

1. Cerebral water homeostasis

Researches have been shown that osmotic changes in brain with hepatic failure lead to cerebral edema. Whenever the brain develops edema, intra cerebral pressure will increase and lead to herniation in brain that can cause coma or death.

Glutamine produced in astrocytes due to detoxification of ammonium in the astrocytes because there is no urea cycle in brain and that glutamine increase the entry of water into brain cells leads to edema in the astrocytes.[100]

2. Brain axonal communication;

There is also clue of the vital function of astrocytes in maintaining

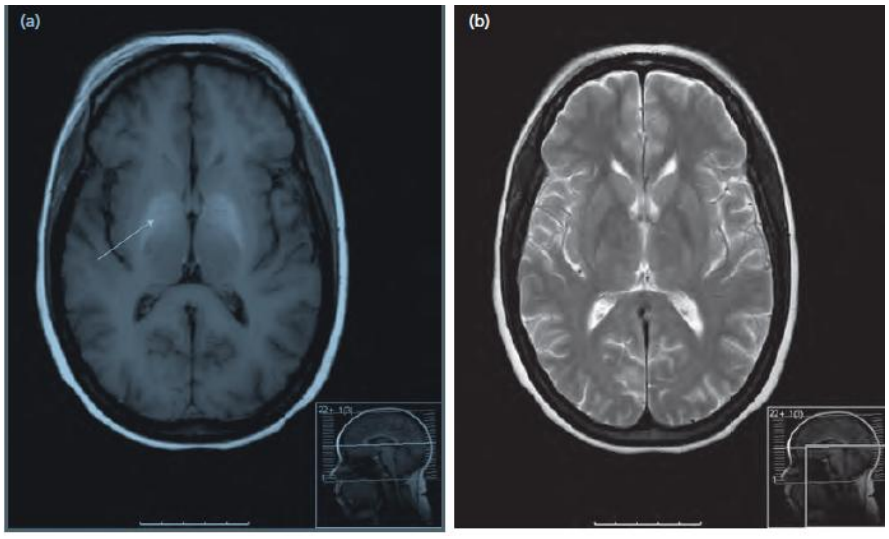

Figure: 9-MRI images T1- or T2-Weighted showing bilateral, symmetrical hyper intensity in pallidus.[91]

Normal axonal activity in HE there is no change in the neurons morphology. The Alzheimer type II brain cells (astrocytes) can show abnormalities-decreased activity of transporters (glutamate), and increased monoamine oxidase (MAO) activity and increased role of benzodiazepine receptor, As a result alterations into communication between astrocytes and other brain cells. For example brain astrocytes synthesized neurosteroids which activates endogenous benzodiazepines receptors and GABA receptors

OTHER IMPORTANT HYPOTHESES

1. Gut –induced neurotoxins

There are neurotoxins produced by gut hypotheses have important key role related to the pathogenesis of HE: most important cause of ammonia production in intestine due to break down of diet protein,

- ***Ammonium.***[96, 97]

Ammonium is main central role to the pathogenesis of hepatic encephalopathy. Ammonia turn out mainly from protein of food and micro organism action in colon, normal person ammonia usually goes to peri portal hepatocytes and converted to urea by urea cycle and few ammonia change to glutamine by venous hepatocytes ,serum ammonia level increase due to ammonia

forming bacteria in gut ,shunting of portal hepatic system, poor function of liver cell, low serum zinc ,decrease muscle mass Brain intake of ammonia raised in DCLD patient ,in brain no urea cycles there ammonia detoxification by the astrocytes many neuron-chemical changes occur astrocytes. There are many other factors that interact with ammonium in brain, causing alterations in the brain cell (cytokine elevations, hyponatremia ,low zinc level in serum and changes in the legends of astrocytes), there by producing neuron-chemical activity which increase the occurrence of HE.

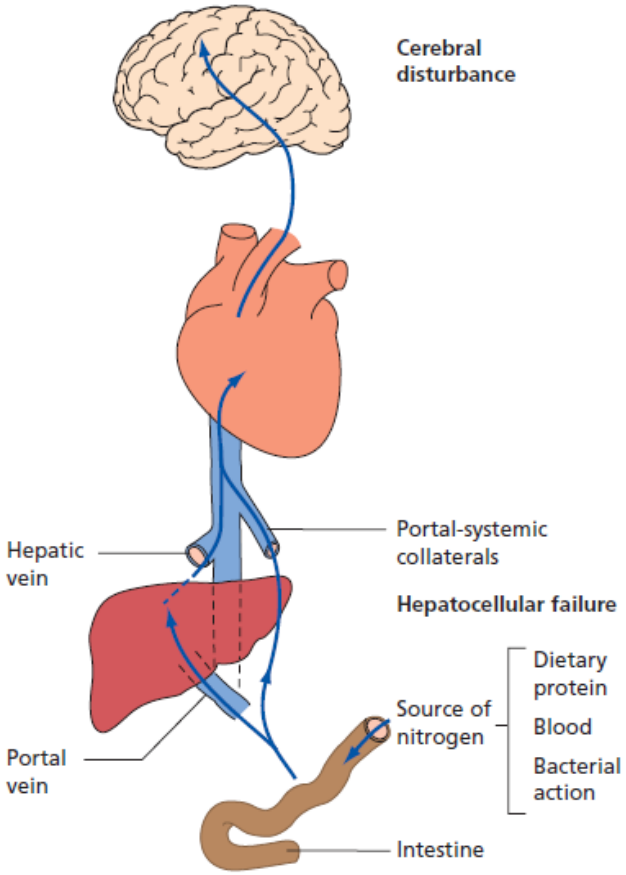

Figure: 10-Gut induced neurotoxin and sources

Further studies consistent with accumulation of toxic levels of ammonia in HE is given by the results of recent studies using (PET) Positron Emission Tomography. The PET studies revealed that the increased cerebral metabolic rate for ammonia in patients with HE was accompanied by an increase in the permeability / surface area product, a measure of blood brain barrier permeability suggesting that in hepatic insufficiency the barrier becomes highly accessible to ammonia.

2. Role of zinc in clearance of ammonia;

Zinc is an important key element of many physiological mechanisms, important co-factor of many urea cycle enzymes like ornithine transcarbomylase, glutamine synthetase and with advanced class of cirrhosis and increasing HE class the zinc level in blood also decrease. Low serum and liver Zn decrease the activity of ornithine trans carbamylase in liver. due to disturbance urea cycle cause increase the ammonia level in blood and raised ammonia level and low zinc level associated with HE and malnutrition ,patient those more sever HE also has more low plasma zinc,

3. Role of Endogenous benzodiazepine;

The role of endogenous BZD in the changes of GABA-ergic neurotransmission is not clearly understood. Trials with flumazenil have not shown significant results.

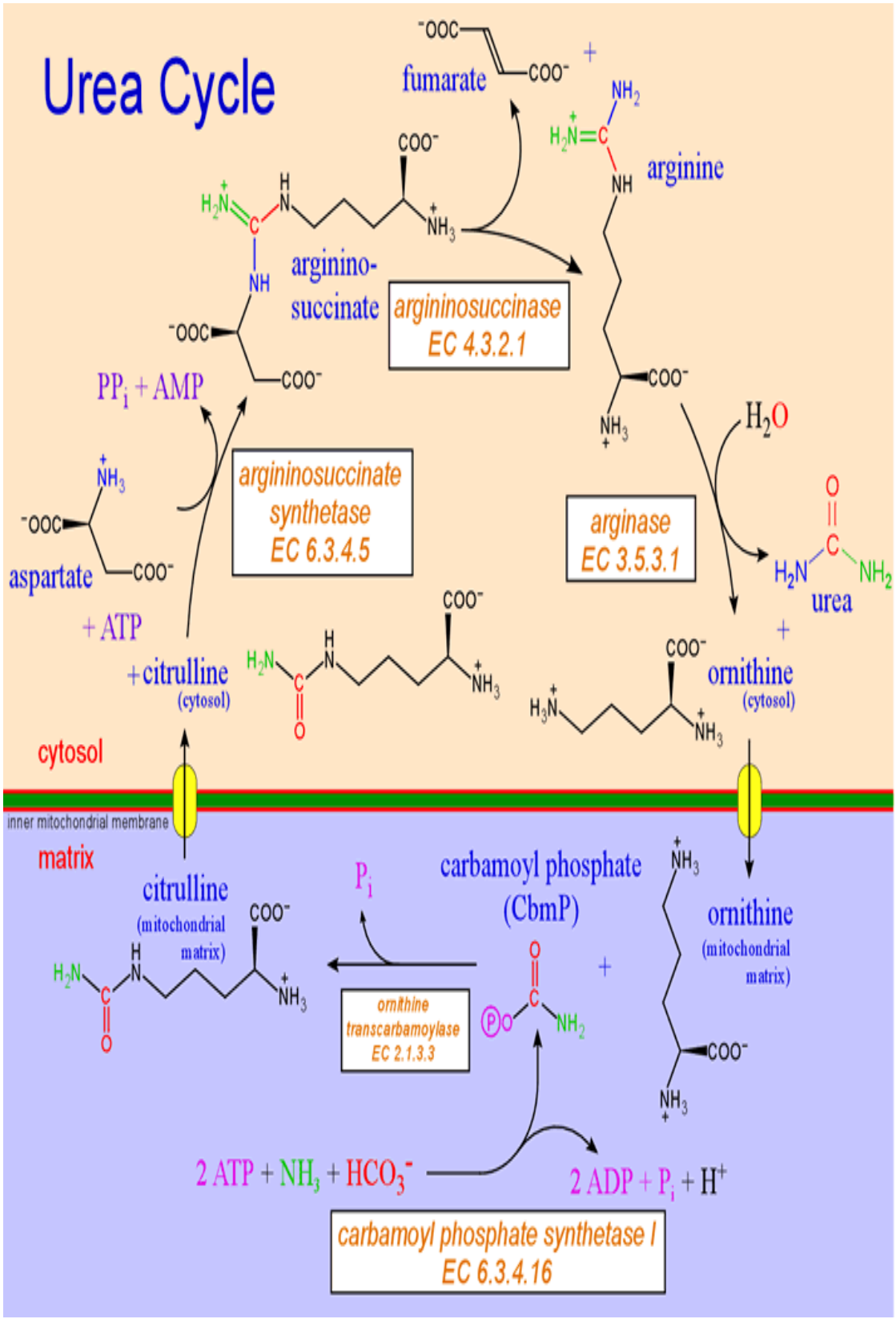

Figure: 11- Normal urea cycle in human

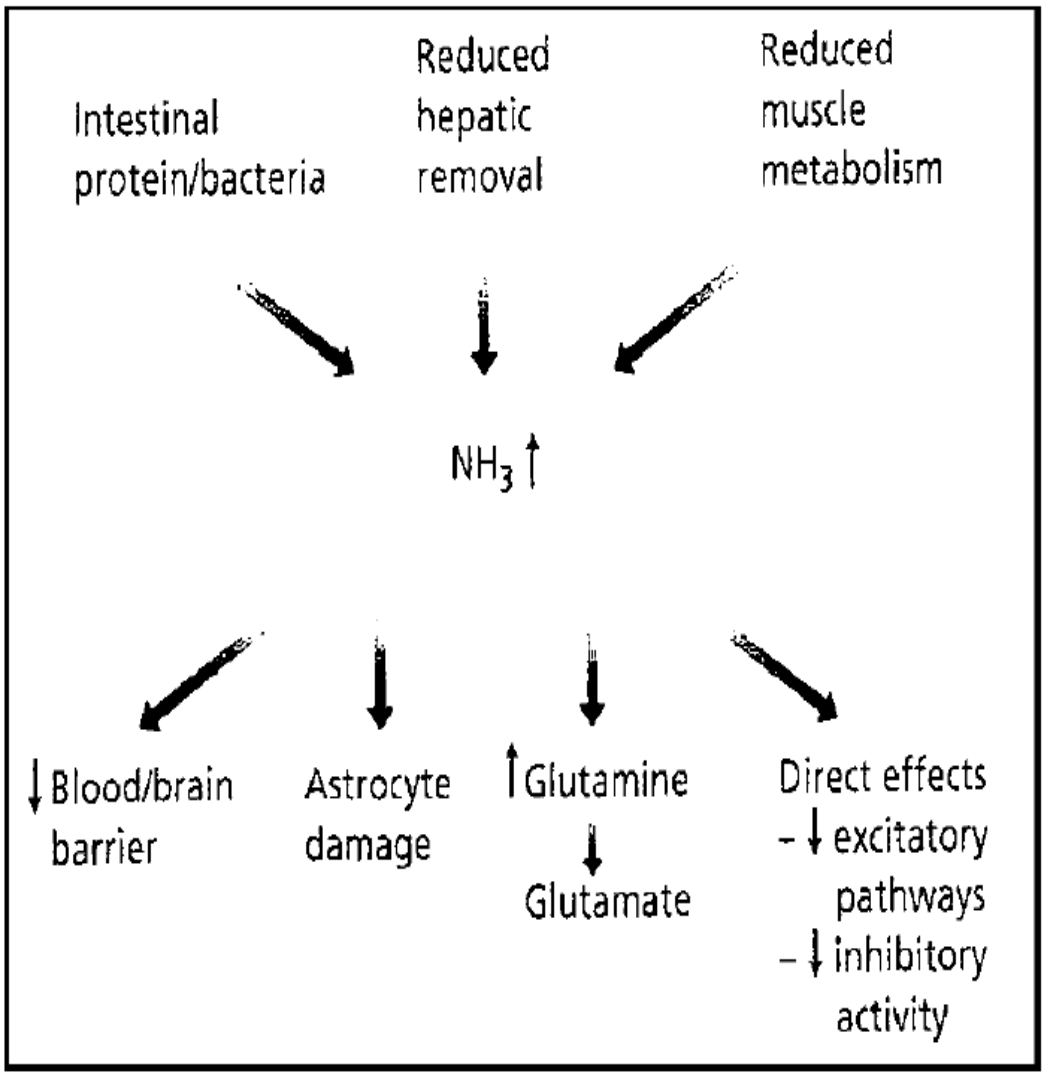

Figure: 12-Ammonia; Key role in hepatic encephalopathy and it's main sources•

4. Change in brain neurotransmitters

Excitatory NT decrease in brain mainly due to high ammonium. Branched chain amino acids (BCAA) decrease in DCLD patient that can increase the entry of other amino acids in to brain. Those amino acids are pre source of other brain transmitters that affects Glutamine formation.

BCAA is of important role in ammonia clearance, that the amino acids have a direct role in ammonia detoxification in muscle, increasing. Many other brain transmission cycles also affected development of HE,

1) Serotonin (5-HT)-increase in HE

2) Catecholamine-reported low in patient dye due to HE

3) Acetylcholine- low

4) Other e.g. opioids, steroid, melanin, histamine

Most of cirrhosis have poor nutrition due to malnutrition and low oral intake that patient may have microelements and vitamins deficiencies, those are also additive factors to turn of events like recurrent HE.

For example zinc deficiency have important role in development of HE. Zinc supplementation a dose of 600 mg/day for short period useful in improvement in HE. Many studies have been suggested role of zinc in recovery HE.

4. Microorganism over growth;

However**,** some studies suggested that colonization of bacteria in gut has been suggested role in development to MHE, but still it is not clear, need more studies.

Conclusion, pathogenesis of HE due chronic or acute liver cell failure, collection of gut derived toxin and portal-systemic shunt.

The precipitating key factor (absence specific cause) is an increase level of serum ammonium. The pathogenic mechanism includes the production of false neurotransmitters, facilitated sensibility of neurons by γ-amino butyric acid (GABA), increases in the plasma endogenous benzodiazepines, failure of urea cycle due to low enzymes activity as a result of low level of zinc in plasma and excessive manganese deposits on the basal ganglia.

CLINICAL CLASSIFICTION OF HE

Generally, we can diagnose overt HE easily, but for diagnosis of minimal hepatic encephalopathy (MHC) need neuropychometric test.

Clinical symptom based stages as shown below stage- II shows symptoms such as moderate confusion and more behavioral abnormality, in stage- I minimal behavioral changes may be present, like mild confusion, euphoria or mild depression. In advanced HE stages patients may be present with global confusion, drowsy and unconscious state.

Also some non specific changes in electroencephalographic (EEG) can be found (triphasic waves and delta activity).

Categorization HE on the basis of etiological causes

Type-A: Acute onset hepatic failure

Type-B: Due to shunting Portal-systemic without intrinsic liver disease (more frequent)

Type-C: As result of PHT and DCLD with Porto-systemic shunts

Classification and grades of hepatic encephalopathy according severity of clinical manifestation;

Grade 0-Minimal hepatic encephalopathy (MHE);

Neuropsychometric and psychological test need to diagnosis of MHE, changes occur in test.

Patient not have clinical symptom.

Construction aprexia may present

Grade I- Loss of awareness,

Anxiety or euphoria or depression,

Low attention,

Monotonous voice

Sleep cycle disturbances.

Grade II- Apathy and Lethargy and/or confusion.

Not orientation about time,

Asterixis, triphasic waves may be on EEG

Grade III- Severe confusion/ irrelevant speech,/incoherent language

Drowsy but responds to stimuli

Asterixis, triphasic waves on EEG

Grade IV- Coma, initially can respond to painful stimulus

Later no responds to deep pain and Delta wave in EEG

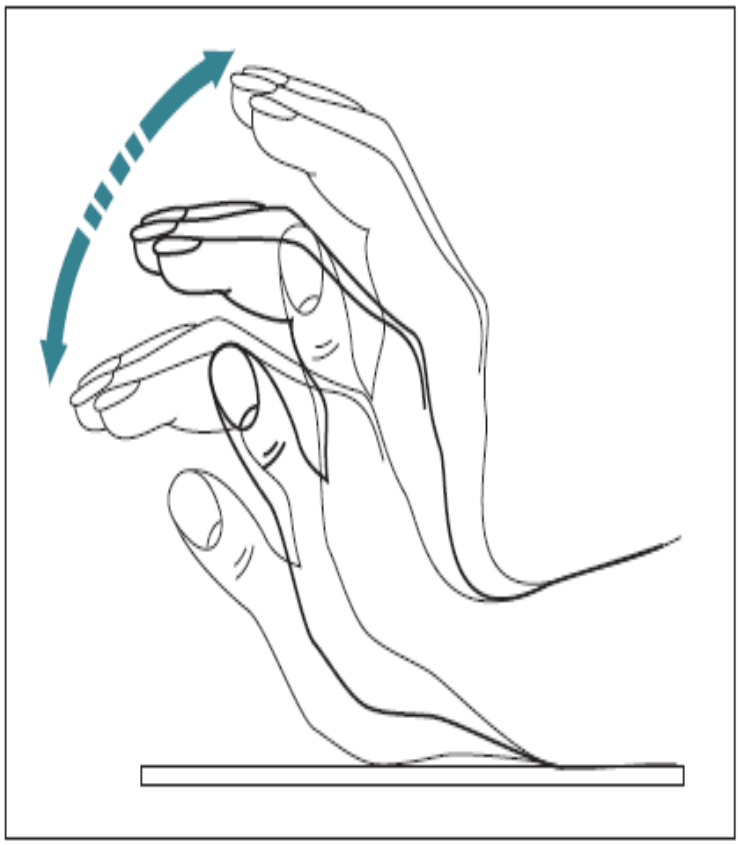

Figure: 13 -flapping tremor in HE

Factor associated with precipitation of HE;

The hepatic encephalopathy is one of common complication of DCLD. The cirrhosis patient developed complication like HE due to presence of various precipitating factors.

Table 2-precipitating factors of HE. [1, 93, 94]

Nitrogen product	Drug	Metabolic	Others
GI Bleeding	Diuretics	Hypokalemia	Infection
Constipation	Opiates	Hypontremia	Renal failure
High protein	Sedative	Alkaiosis	Surgery
Azotamia	Diazepam	Dehydration	Hepatopathies
H.Pylori	Phenol	Low zinc	Magnese
Uremia	Hepatotoxic	Hyperkalemia	Short fatty acid
Microorganism		Hypoxia	

Episode of hepatic encephalopathy possibly occur as result of one or more precipitating factor, as described above table.

Hepatic encephalopathy most common precipitating factor is UGI bleeding and infection.

The clinical course of HE on the basis on frequency and form of occurrence of HE in the same patient can be present as like hood three types:

Episodic HE-Acute onset

Associated with precipitating factors

Recurrent encephalopathy;

When patient again present with in 6 month or less time.

Persistent HE:

Cognitive disturbance

Extra-pyramidal manifestations,

Sleep-pattern changes that can be either mild or severe,

But always continuous

4. Minimal HE:

Sub-clinical cases,

Diagnosis by psychometric score

HE is manifested in different forms and may be occurred with some neurological manifestations, can be present with focal deficits.

Usefully, clinical features are contributes due to cerebral edema.

That brain edema associated with the clinical picture HE and high mortality in the patients with HE.

Table:3 The Glasgow Coma Score (GCS) - For diagnosis of unconscious level

Variable Score	Eye opening	Motor response	Verbal response
1.	Spontaneous	Follow oral com	Fully orientation
2.	To oral command	Localized pain	Disorientation
3.	To pain	Withdrawal to pain	Moderate confusion
4.	No	Abnormal flexion to pain	Severe confuse (incomprehensive)
5.		Extensor response to pain	No response to commands
6.		No response	

Poor attention and changes of brain state may occur as behavior abnormality , memory disturbance, confusion, semi coma and to coma; also, occurred with various of n signs include a rigidity ,abnormal reflexes increase DTR ,extensor planter ,astrexis and rarely, convulsions.

The earliest sign of encephalopathy is a disturbance in the sleep cycle. High ammonium concentration is a key factor in the

diagnosis of HE. But the predictive value of ammonia is very less in DCLD patients,

Ammonia level in arterial blood with adjustment ammonia value with pH we can increase predictive value of ammonia, but these tests may not be possible in all center.

Recently, some studies have shown association between ammonia level in arterial blood and its correlation with development of brain herniation in FLF.

Few other studies have suggested that more ammonium level (>300 mg/dl) found in advanced hepatic encephalopathy (stages III and IV), these patients are associated with brain herniation.

High ammonia level in blood not associated with change in liver function Also, it has been shown by many study that ammonium levels correlate with the severity of HE but not associated the with treatment response. Brain imaging also important role in diagnose MHE stage I and stage II Brain MRI can demonstrate basal ganglia manganese deposition and showing globus pallidus.[90]

Computed tomography in advanced HE usually shows presence of atrophy or brain edema. Positron emission tomography

studies images reflecting physiological and biochemical changes in brain processes.

Finally, MRI spectroscopy suggests evident the rising glutamine spike in brain and low choline and myo-inositol.

NEUROPSYCHOLOGICAL FOR MHE.[91, 92]

1) Line drawing
2) Numeric connection
3) Digital symbols and
4) Points following.

These test called PHES Psychometric hepatic encephalopathy score (PHES) and should be complete in ten minutes.

The objective is to evaluate the reaction time and the visual construction, accusiocity, memory, concentration testing across neuropsychological domains is possibly the optimal approach to identify selective abnormalities in areas such as attention and fine motor function.

However the need for shorter evaluations has led to the use of four tests in most case. A specific test like the line tracing, the NCT, the serial dotting tests has a good specificity for HE compared with other encephalopathy.

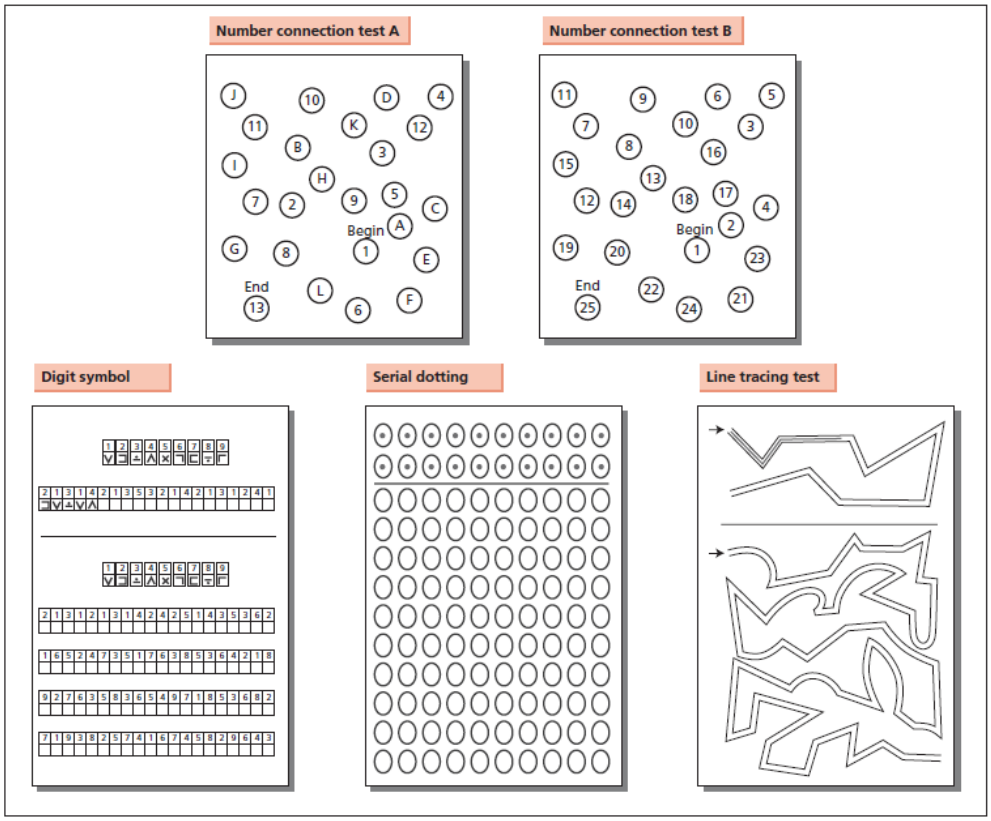

Figure: 14- Psychometric test for MHE; Pencil and paper test, Digital symbol test, and Line tracing;

NEUROPHYSIOLOGIC TESTS:

- ❖ Electroencephalogram (EEG)
- ❖ Evoked potentials

Both, the EEG and evoked potentials, can be used for the detection of minimal HE, on principle. Because of the more sophisticated technical requirements of evoked potential studies the EEG has been used, predominantly. The major finding is a general decrease in wave frequency and an increase in wave amplitude. First, so called theta waves with a frequency between 4 - 7 cps

occur, and then these theta waves predominate and are committed by delta waves with a frequency of 1 - 3 cps, Completely there is loss of wave amplitude and a flattening of the curve. These abnormalities are not restricted to manifest encephalopathy but may be found even in cirrhotic without clinical signs of encephalopathy. It must be emphasized, that there is no close correlation between the grade of HE and the degree of EEG abnormalities.

Compared to psychometric tests the sensitivity of the EEG for the diagnosis of minimal HE is limited. The EEG is useful for follow up examinations. Predominantly Clinical improvement in patients with HE is often preceded by an increase in EEG frequency, while on the other hand an impending HE episode may be foreseen when the EEG frequency of a patient decreases. This is true even if a patient with an individual frequency of 12 cps for example presents with an 8 or 9 cps EEG, which is within the normal range per definition but is undoubtedly pathological, compared to the patients individual standard frequency.

Finding in EEG and evoked responses are nonspecific and not useful in diagnosis of HE. The simplest assessment in hepatic encephalopathy is to grade the degree of abnormality of the conventional tracing.[89]

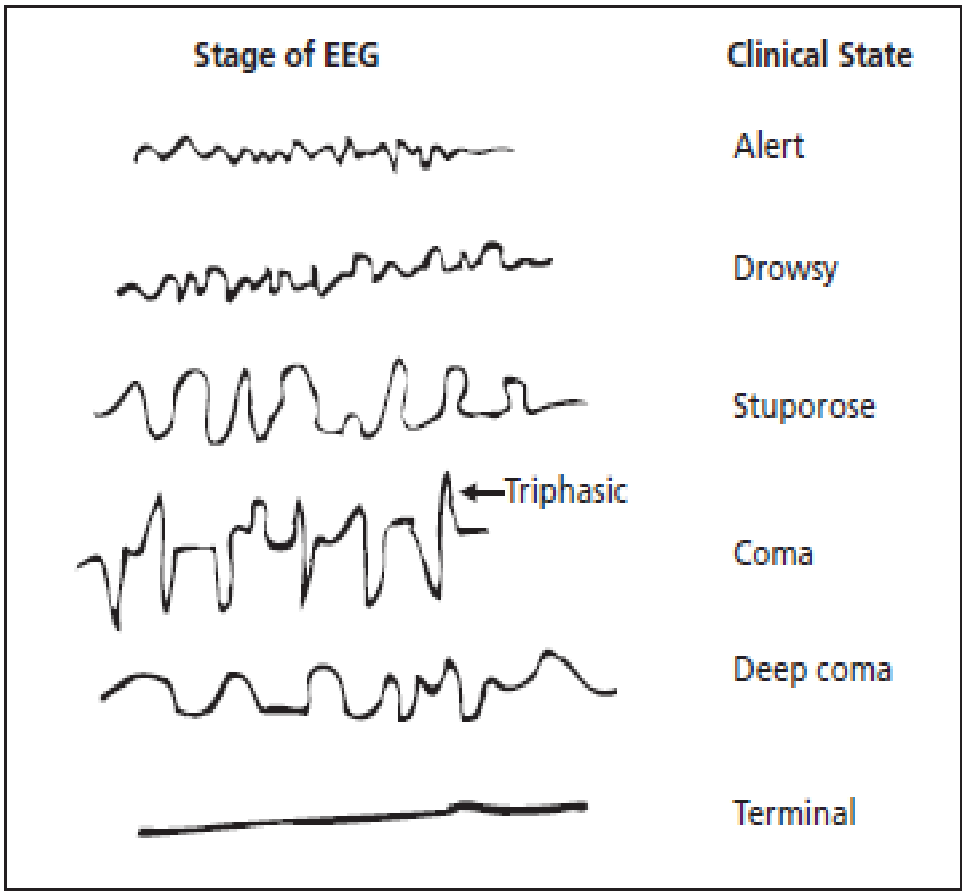

Figure: 15- Changes in EEG in patient with HE with present in different stages

MANAGEMENT AND THERAPY OF HE:

The treatment of DCLD patients with overt HE includes establishing the treatment protocol. In recurrent HE the main objectives are avoid the acute episodes, while a patient with chronic HE our aims are towards improvement in quality of life and persistent symptoms.

The treatment of HE should be added with the treatment of the other complications of DCLD.

In DCLD patient's presence complication HE is indication of poor prognosis and hence should be keeping as candidates for liver transplantation.[33]

Routine treatment aims for patients with HE is the importance of applying some general supportive measures to patient like protection of air way, nursing care, bed care ,proper feeding during the period of unconscious and abnormal mental state,.

It is very essential to pick up the acute precipitating factors and treat them aggressively.[32]

TREATMENT AIMS

Correction of precipitating factors

Proper management of HE needs identification and aggressive treatment of precipitating etiology. Mostly the precipitating incident is either UGI bleeding or infection. Some other precipitating factors listed above include excess protein load dietary intake, drugs acting on brain acting as sedatives, analgesics, and dehydration or electrolyte disturbance.

Laboratory and radiologic investigations can also help in identifying precipitating factors.

- Dehydration should be treat by stop of diuretics and adequate IV fluids.38
- GI bleeding can be treating with blood transfusion. Long term treatment for variceal bleeding are-
  - Endoscopic sclerotherapy (ES)
  - Endoscopic variceal ligation (EVL)
- Drug use treatment for variceal bleeding;,
  - Octriotide
  - Terlipressin

The patient with massive ascites paracentesis should be performed and send for cell count, culture and gram staining to evaluate for spontaneous bacterial peritonitis (SBP).

Infection patients of HE with fever and abdominal pain suggestive infection should evaluate for SBP and start with antibiotics treatment. Practice guidelines for ascites management have included standardized methods for the fluid tap technique and for ascitec fluid analysis. Some studies have been shown that

clinical risk factors for infection and recurrent SBP suggestive antibiotic prophylaxis.

Recently trial in DCLD patient use of albumin and cefotaxime compared with antibiotic alone was associated with significant improvements in survival rate and renal function among selected patients.

Hypokalemia should be treated with oral or IV potassium.

HE precipitated by dietary protein intake so diet should be balanced for patient with DCLD and use sedatives avoid in patients with HE,

D/D OF HEPATIC ENCPALOPATHY;[81]

Table4- differential diagnosis of HE

Overt HE or acute confusional state
Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Other presentations
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea

We should exclude as well other causes of abnormal barin function

MEDICAL THERAPY: [95]

Nonabsorbable disaccharides: [102]

There are lactulose and lactitol. Role of these agents in treatment of HE is to decrease the ammonia production and absorption in GI tract,

Lactulose act via three mechanisms;

1) Laxative effect- these agents increase the movement of ammonia from the portal circulation into the colon, and interference with the uptake of glutamine by the intestinal mucosa and its subsequent metabolism to ammonia.

2) Increase uptake of ammonium by microorganism

3) Decrease production of ammonia-By change the glutamine uptake via intestinal mucosa.

Lactulose- as syrup with dosages of 10 to 30ml given 3 times a day. Patient should pass 2 to 3 soft bowel movements daily. Lactulose given by mouth reaches the large intestine in caecum, where it is broken by bacteria mainly to lactic acid that lead to raised osmotic volume of the colon, low fecal pH.

Promote the growth of lactose fermenting bacteria e.g. bacteroids, which are use ammonia and suppressed ammonia forming bacteria. The colonic fermentative bacteria prefer lactulose to blood when both are present. Side effects of lactulose are diarrhea and intestinal pain, fluctuance.

Non absorbable disaccharides are the first line therapy for treatment of acute HE and improvement in symptoms occurs in more than 80% cases. A placebo controlled trial showed lactulose successfully improve MHE cognitive function or quality of life in DCLD patients with minimal hepatic encephalopathy.

Lactitol- is a second generation disaccharide easily produced in chemically pure crystalline form and available as powder. It is not broken down or absorbed in the small intestine, but is metabolized by colonic bacteria. A dose of 20-100 gram/day is well tolerated and effective

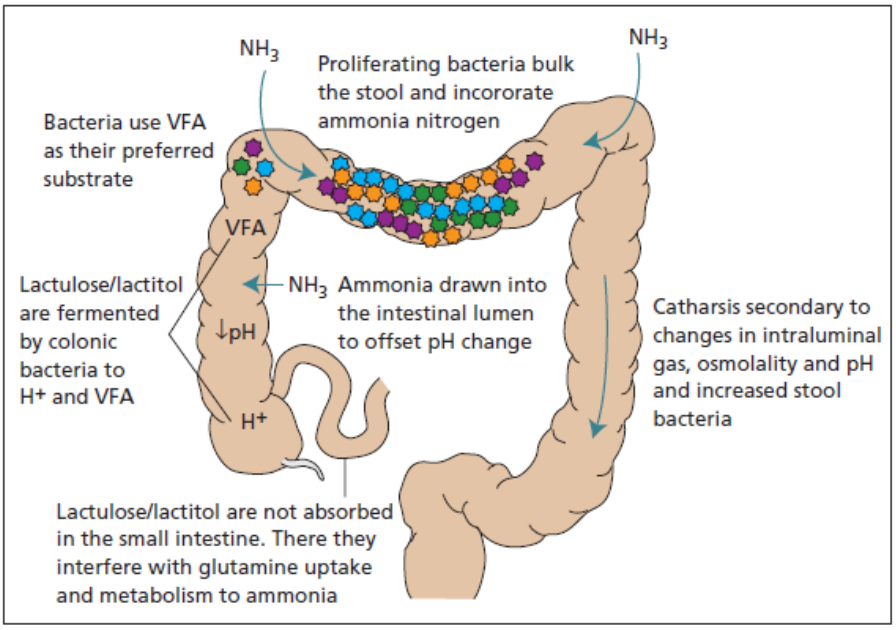

Figure: 16 –nonabsorble disaccharides metabolism in intestine by bacteria

Antibiotics: [103]

Neomycin and Metronidazole decrease production of ammonia in intestine by acting against bacteria.

Neomycin- is used for short period due to its side effects on long term use (4-6 gram daily in divided doses).

Metronidazole -200mg three times a day per oral is as effective as neomycin. Prolonged use leads to dose related nervous system toxicity.

Rifaximin: It is an oral antibiotic with fewer side effects and no known drug interactions. Poorly absorbed (<1%) .It has been found very safe and highly effective in patients with stage I to II HE.

A blind controlled study compared Rifaximin 1200 mg per day to Neomycin 4 gram per day, after 21 days of treatment the symptoms of HE and serum ammonia levels were reduced in both group, although reduction in serum ammonia were significantly greater with Rifaximin.

Another study Rifaximin 1200 mg/d compare with lactitol 60 g/d administered for 2 weeks showed significantly improvement in 80% symptoms of both groups.

Zinc role in treatment of HE: [61,62]

Is an essential trace element which plays an important role in the regulation of protein and nitrogen via urea cycle As a co-factor of many enzymes use in urea cycle, Zinc deficiency has been implicated in the pathogenesis of hepatic encephalopathy as decreased serum zinc levels and low zinc level associated with in inverse correlation with blood ammonia levels in those patients. Zinc short term therapy improved ammonia clearance via urea cycle, that decreased serum ammonia level in cirrhosis patient and improve his/her neurophychiatric manifestation. A double blind randomized placebo controlled study of zinc acetate 600 mg/d for 7 days demonstrated improved mental status that was associated with increase in serum zinc levels.47 In another study after 3 months of

supplementation with 600 mg zinc sulfate daily there was normalization of serum zinc levels and improvement in neuropsychiatric testing in hepatic encephalopathy .

OTHER THERAPIES:

Benzodiazepine receptor antagonists:

In a study of cirrhotic patients, IV Flumazenil was compared with placebo. The intervention group showed improvement in neurological scores in 18% of patients with stage 3 HE and 15% of those with stage 4 HE, as opposed to 4% and 3% of placebo treated patients respectively.

LOLA (Ornithine L-Aspartate) [105]

LOLA has been demonstrated to reduce blood ammonia levels by providing substrates for the intracellular conversion of ammonia to urea and glutamine.

Sodium benzoate

It may be beneficial in the treatment of hepatic encephalopathy by increasing urinary excretion of ammonia.

Probiotics:

Probiotics are defined as biologically live microorganism dietary agents. These are effective in HE on the host beyond their nutritive value. The mechanism of action of probiotics in HE is

achieved to be the change the substrates for potentially pathogenic microorganism, and the aim of fermentation end products for potentially beneficial bacteria.

BCAA (Branched chain amino acids) . [104]

DCLD patients usually have low plasma BCAA, which have role in change in brain transmitter, needs more studies.

Nutrition:

Guidelines given by the European Society for Nutrition and Metabolism suggested that patients with cirrhosis should have an energy intake of 30 to 40 kcal/kg body weight per day and daily protein intake of 1.3 to 1.5 gram per kg body weight.

The concept of protein restriction diet for the treatment of HE was based on old uncontrolled studies made nearly 50 years past.

MATERIAL AND METHODS

This crossection study was conducted in Institute of Internal Medicine at Rajiv Gandhi Government General Hospital and Madras Medical College,Chennai

Duration of study -6 months(April 2014 to September 2014)

Sample Size-75 cases

Inclusion Criteria

- ❖ patients diagnosed as Decompensated Chronic Liver Disease presents with Hepatic encepalopathy.
- ❖ Including minimal HE
- ❖ DCLD due to all etiology
- ❖ Age >20 years
- ❖ Both sex
- ❖ Written informed consent

Exclusion Criteria-

- ❖ Metabolic causes of encepalopathy
- ❖ Altered sensorium due to head injury and stroke

- ❖ Psychiatric disorders
- ❖ Alcohol with drawal state
- ❖ Acute alcohol intoxication

Data Collection

Study subjects are both sex group and above the 20 year age. DCLD pateints admitted with complication hepatic encepalopathy , The diagnosis of HE based on history taken according to a Questionnaire, a detailed clinical history of subjects taken regarding present and past illness.Quetions asked about altered sleep pattern anxity depression,euphoria,altered sensorioum dysoriention and cofusion,history about pracifitating factors also taken like UGI bleedin,fever ,diarrhea ,abdominal pain abdominal distension,constipation ,jaundice, malnutrition and high protein diet.

Datail clinical examination for sign of liver faliure like Ictrus, Pallor, Spider nevi,Palmer erythema,clubbing ascitis and pittng edema

Persional history for alcohol intake and duration of alcohol abuse,drugs abuse and smoking.

Grading of HE by

- Clincal history ,
- PHES(Psychometric hepatic encepalopathy score),
- Astrexis
- WHC(West hevan classification)
- GCS(Glaow coma score)

Clinical grading of HE

Table 5-WHC Grade of HE

Grade	Clinical sign and symptoms
MHE	Alteration in psychometric test ,construction aprexia with out clinical manifestations
Grade-I	Loss of awareness Euphoria or anxiety Lack of concentration Altered sleep pattern
Grade-II	Lethargy, slurred speech Disorientation for time,persnality changes ,Astrexis
Grade-III	Drowsy, Confused Respond to stimuli Bizarre behavior
Grade-IV	Coma Not respond to pain

For each pateints blood investigations

- ❖ Serum zinc level
- ❖ Complet blood counts
- ❖ Liver function test
- ❖ Renal function test
- ❖ PT/INR

All pateints also classified by Child's score based on following paramitters-

Table-6 Modified Child's classification

Parameters	Numerical Score		
	1	2	3
Ascites	none	slight	moderate to severe
Encephalopathy	none	slight to Moderate	moderate to severe
Serum bilirubin (mg/dl)	<2	2-3	>3
Albumin (gm/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time	1-3	4-6	>6

Total score=15

5-6==A

7-9 ==B

9-15 ==C

Method use for Serum Zinc estimation-

Reagents =

- Diathizone-100 ml diathizone(0.1%) was mixed with 100ml of 0.1ml NaOH preoared daily for use
- Pottasium iodide powder
- Trichloro acetic acid
- Saturated Tris solution
- HCL 6N=60 ml of acid diluted with 100ml water
- NaOH 4N=40 grams NaOH in 100ml of water
- Standerds solution of Zinc

Principle –Dithizone (fresh prepration) froms a yellow coloured complex with Zinc tris and buffered tricholoro acetate with centrifugated serum. Other minor elements separated by insoluble iodine and HCl before complex formation of Zinc.that yellow coloured complex measured by spectrophotometry.

Procedure- Three test tube were used and marked as standard, blank and unkown. 3ml standard zinc solution in standard,3ml distilled water in blank and 3ml sera in unknown tube in pipetted,

mixed and kept in room tempreture for 10 min and centrifuged at 3600 rpm for half hour after that and 0.3ml of 10N NaOH added and kept stand for 10 min.all supernatant transferred to separete tube and mixed 0.5ml 0f HCl and 0.5ml of diathizone reagent . The yellow colour formed and read at 555nm after 5 min.

DATA ANLYSIS AND OBSERVATION

Table 1-Sex distribution

	Frequency	Percent
Male	72	96.0
Female	3	4.0
Total	75	100.0

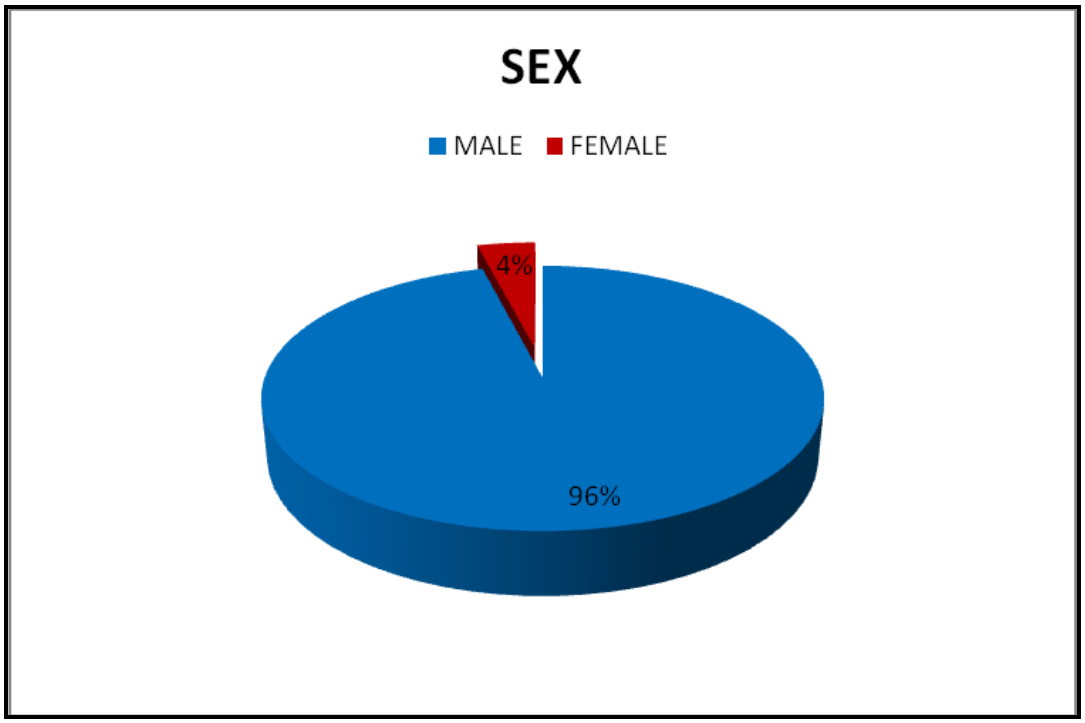

Figure 1 -sex distribution

In our study total 75 cases, including 72 (96%) and 3 female (4%). Hepatic encephalopathy more common in male (96%)

Table-2 Age group distribution

	Frequency	Percent
< 30year	0	0
30-50year	47	62.7
>50 year	28	37.3
Total	75	100.0

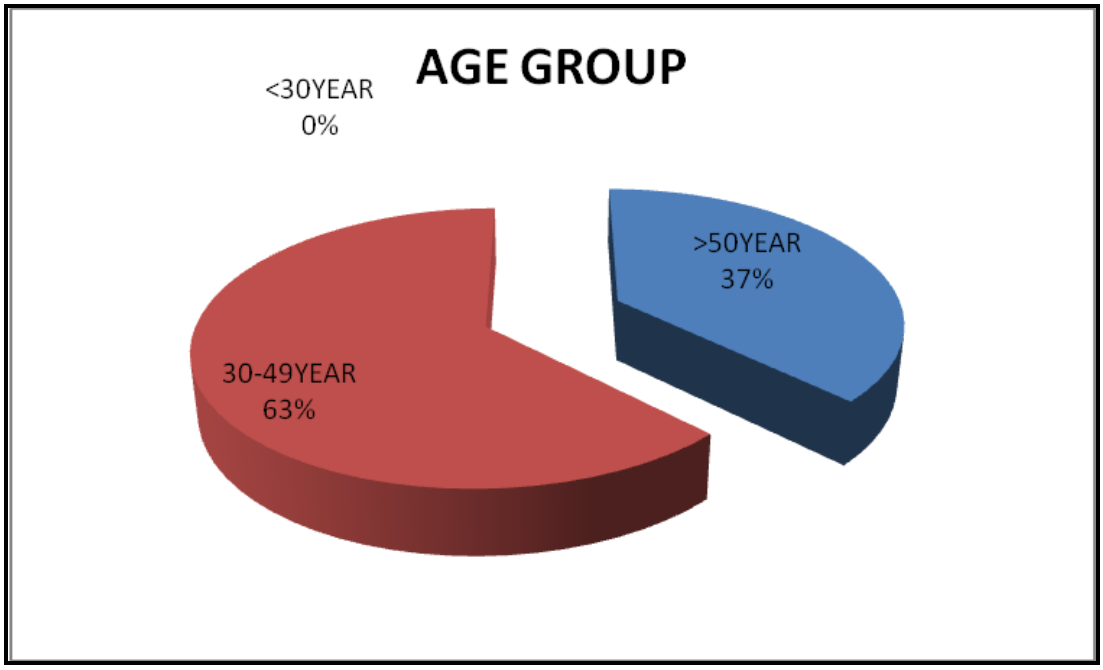

Figure -2 Age distribution

In our study hepatic encephalopathy more common in middle age group between 30-50 year age (63%)

Table3- Mortality during the course of treatment in hospital

	Frequency	Percent
Recovered	70	93.3
Expired	5	6.7

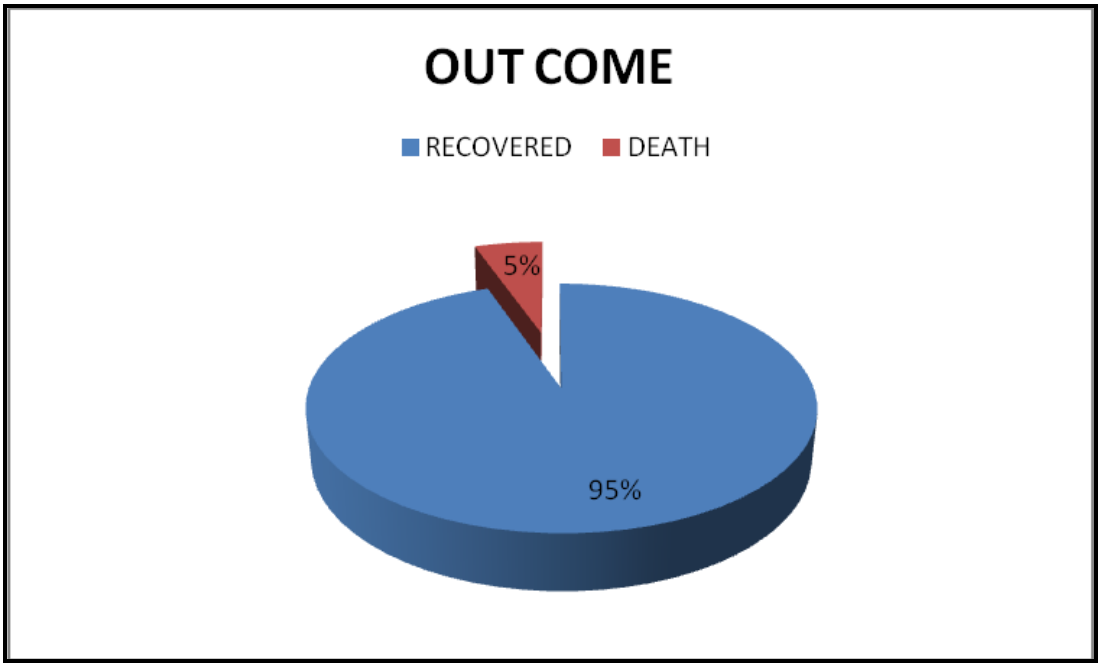

Figure: 3- outcome distribution

In our study 5% mortality in hepatic encephalopathy during the course of treatment

Table4- Etiology of cirrhosis

	Frequency	Percent
Alcohol	68	90.7
HBV	3	4.0
Alcohol and HBV	3	4.0
Wilson disease	1	1.3

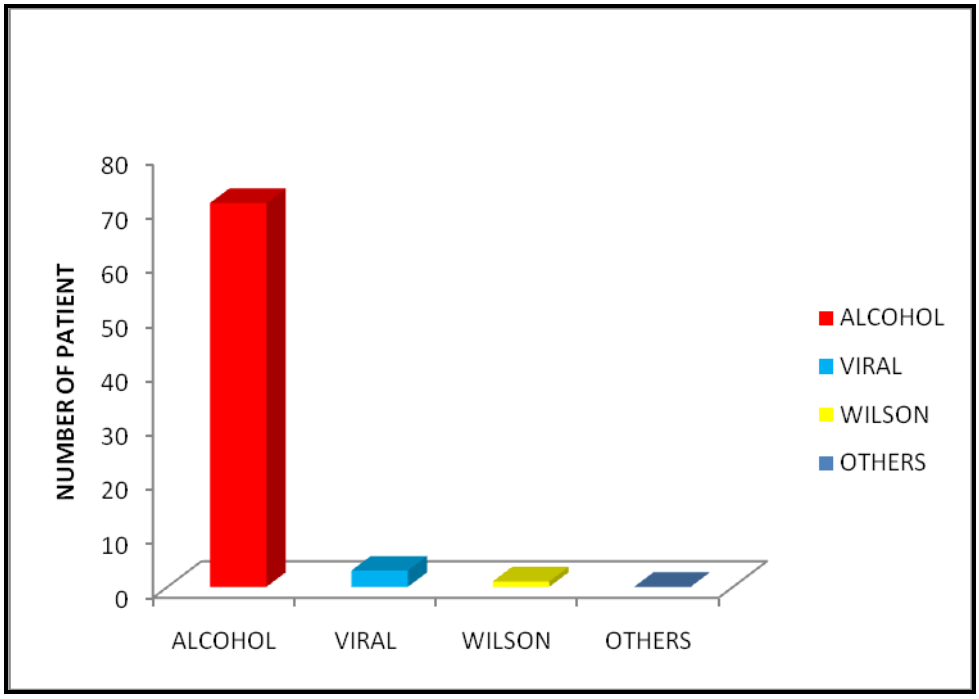

Figure:4- Etiological distribution of cirrhosis

In our study most common cause of cirrhosis is Alcohol (90%).

Table5-Duration of alcohol intake in alcohol related DCLD patient

	Frequency	Percent
Nil	3	4.0
>= 10	65	86.7
5-10	7	9.3
Total	75	100.0

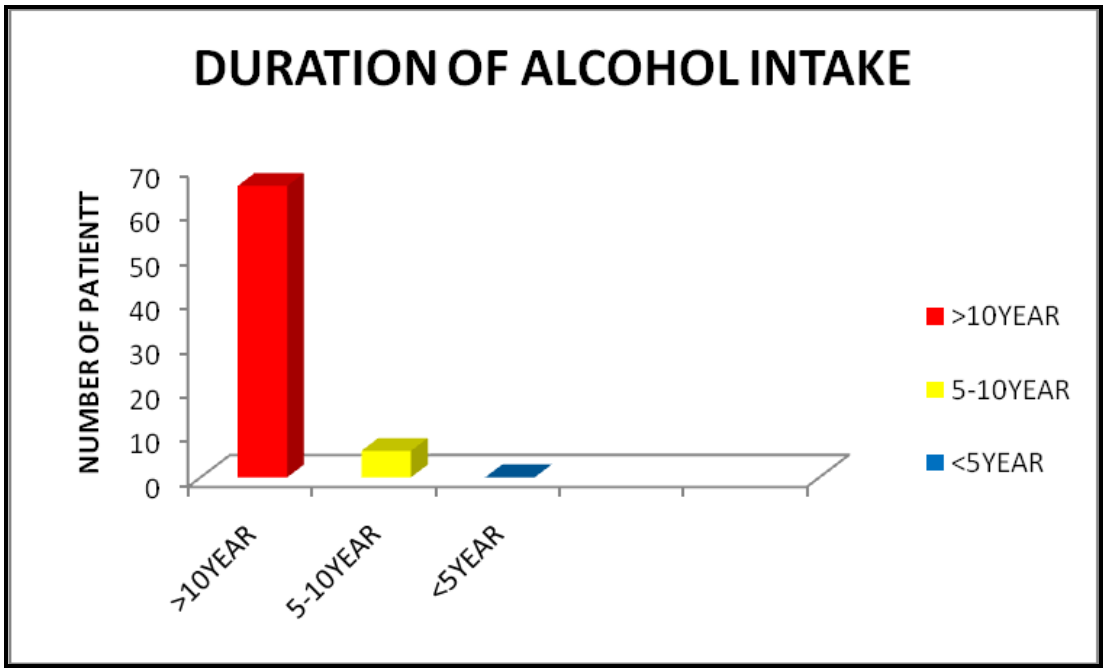

Figure5 –Duration of alcohol intake

In our study 87% patient consumed alcohol more than 10 year duration in Alcohol related DCLD

Table6- Common presenting compliant in DCLD patients with HE

Presenting Feature	Patient
Fever	28
Abdominal pain	42
Vomiting	12
Diarrhea	7
Constipation	41
Ascites	61
Bleeding	34
Pedal edema	49
Disorientation	41
Confusion	14
Coma	4

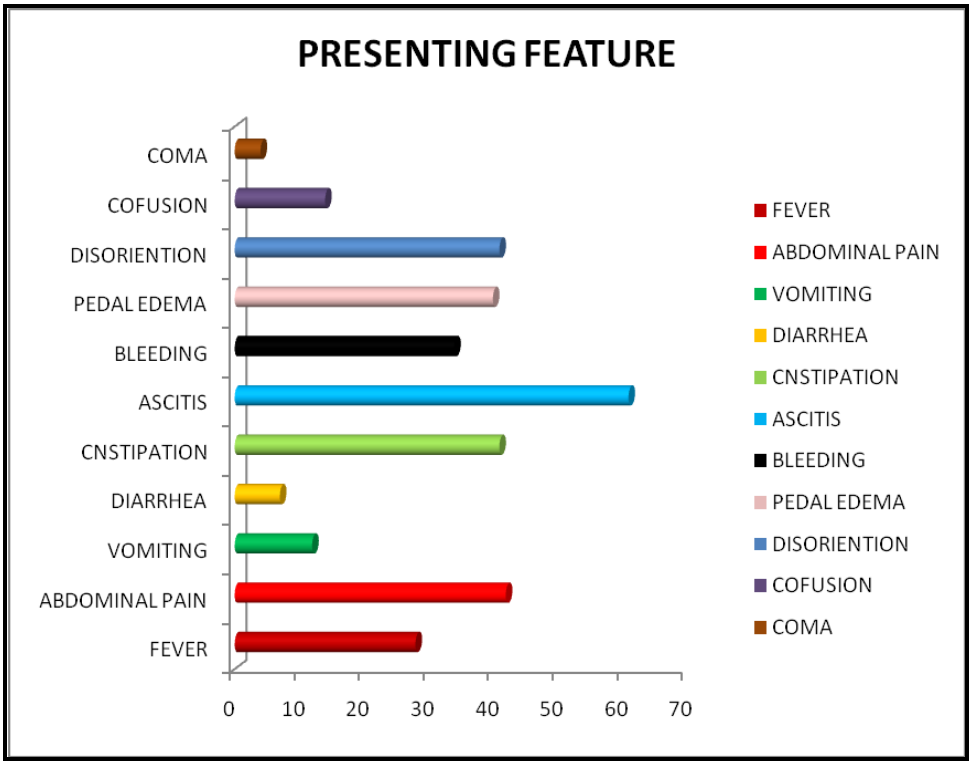

Figure: 6-presenting features in DCLD patient with HE

In our study most common presenting complain of patient ascites other Common features given in table.

PRECIPITATING FACTOR OF HEPATIC ENCEPALOPATHY

Table7- precipitating factors in hepatic encephalopathy

Precipitating factor	Patients
Infection	28
UGI bleeding	34
Constipation	41
Diarrhea	7
Hyponatremia	29
Hypokalemia	13
Hyperkalemia	9
Diueretic	21

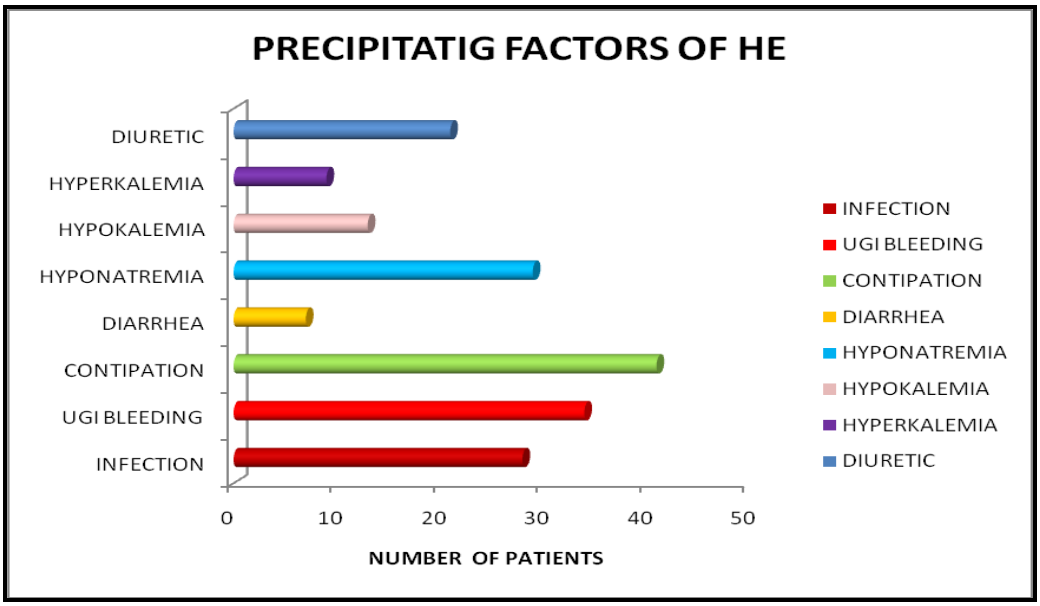

Figure:7-distribution of precipitating factors

In our study common precipitating factors is constipation and UGI Bleeding.

DISTRIBUTION OF PATIENTS ACCORDING WHC CLINICAL GRADE

Table8- patient according WHC Grading

	Frequency	Percent
MHE	10	13.3
Grade I	26	34.7
Grade II	24	32.0
GradeIII	11	14.7
Grad IV	4	5.3

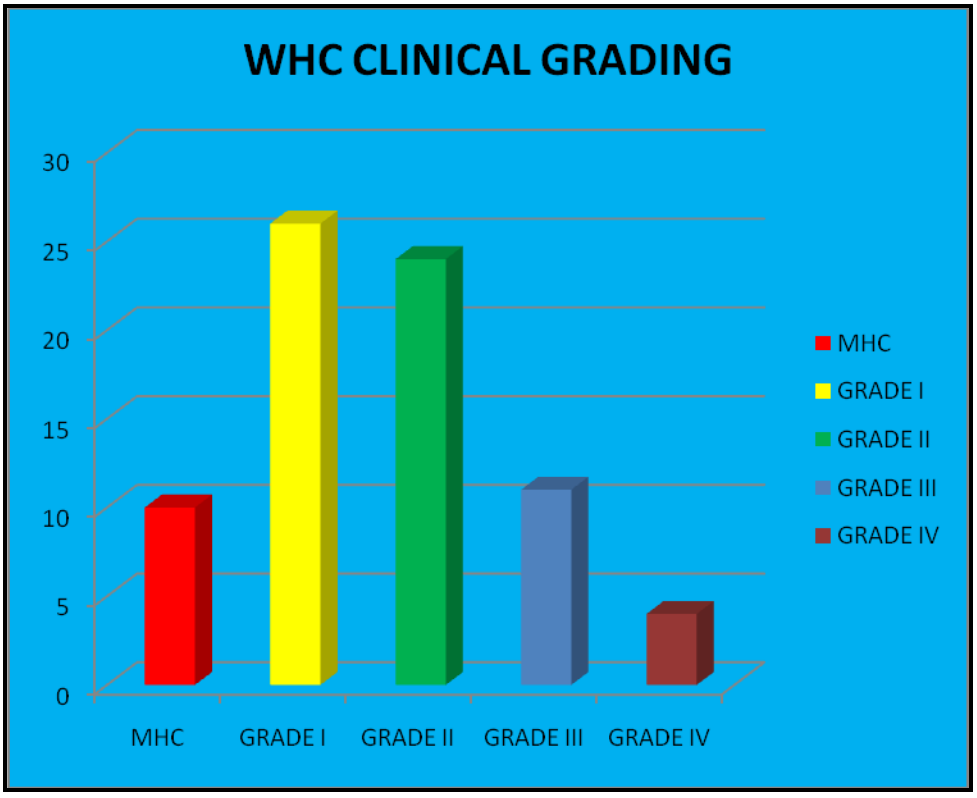

Figure: 8- Distribution of patient according WHC Grading

In our study maximum patients are in grade-I and grade-II (35 &32).

SERUM ZINC LEVEL IN VARIOUS GRADE OF HE

Table9- Serum Zinc level in various WHC grade

			S. Zn					Total
			60-69	50-59	40-49	30-39	< 30	
WHC	**MHE**	**Count**	**7**	**2**	**0**	**1**	**0**	**10**
		% within WHC	70.0%	20.0%	.0%	10.0%	.0%	100.0%
	Grade I	Count	1	8	16	0	1	26
		% within WHC	3.8%	30.8%	61.5%	.0%	3.8%	100.0%
	Grade II	Count	0	2	9	12	1	24
		% within WHC	.0%	8.3%	37.5%	50.0%	4.2%	100.0%
		% within S. Zn	.0%	16.7%	36.0%	50.0%	16.7%	32.0%
	Grade III	Count	0	0	0	9	2	11
		% within WHC	.0%	.0%	.0%	81.8%	18.2%	100.0%
	Grade IV	Count	0	0	0	2	2	4
		% within WHC	.0%	.0%	.0%	50.0%	50.0%	100.0%
		Count	8	12	25	24	6	75
		% within WHC	10.7%	16.0%	33.3%	32.0%	8.0%	100.0%

All DCLD patients have Zn deficiency, low zinc significantly associated With higher grade of HE

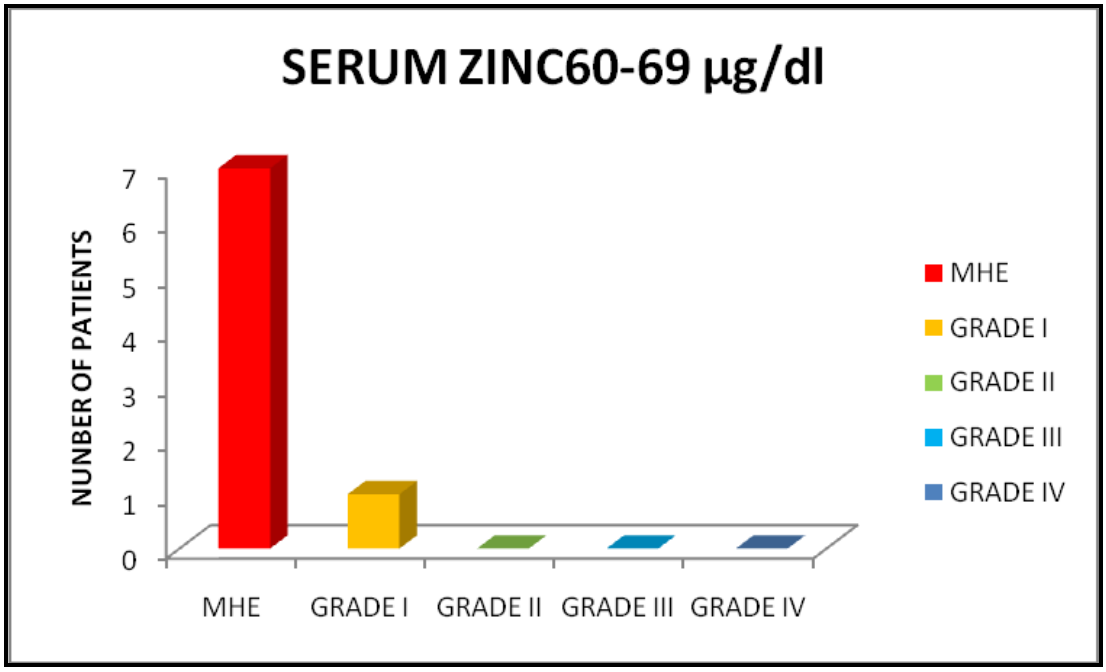

Figure: 9- Serum Zn level (60-69µg/dl) in various grade of HE Maximum patients in MHE in this zinc level group

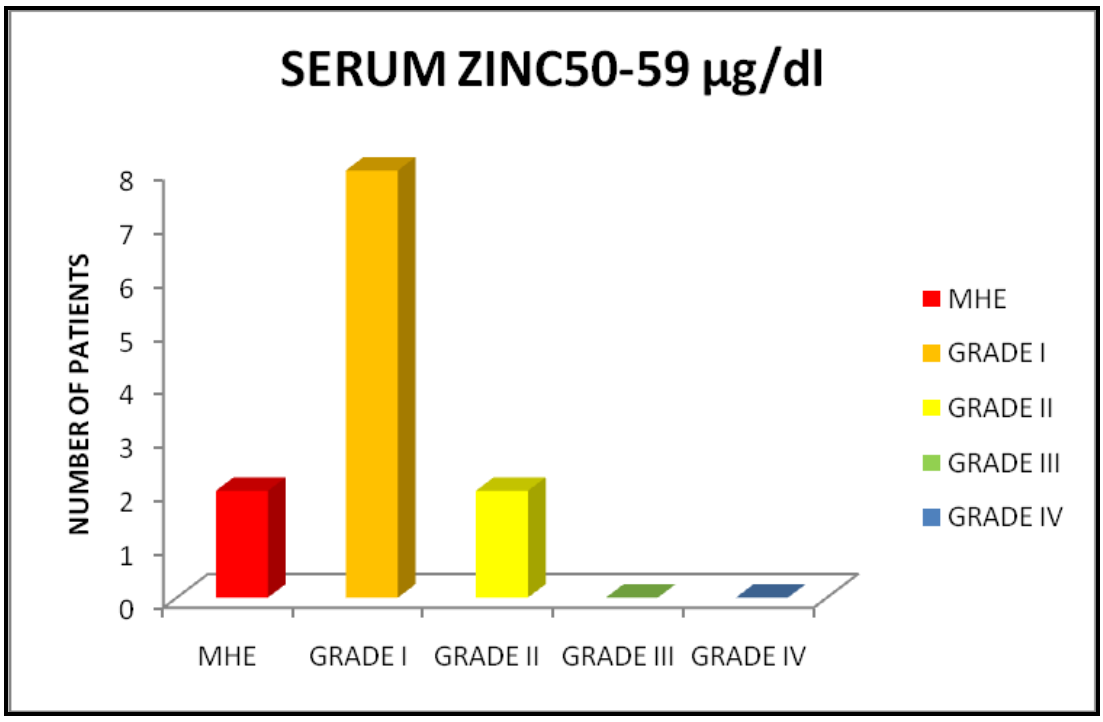

Figure10- Serum Zn level (50-59µg/dl) in various grade of HE Maximum patients in WHC grade-I in this zinc level group

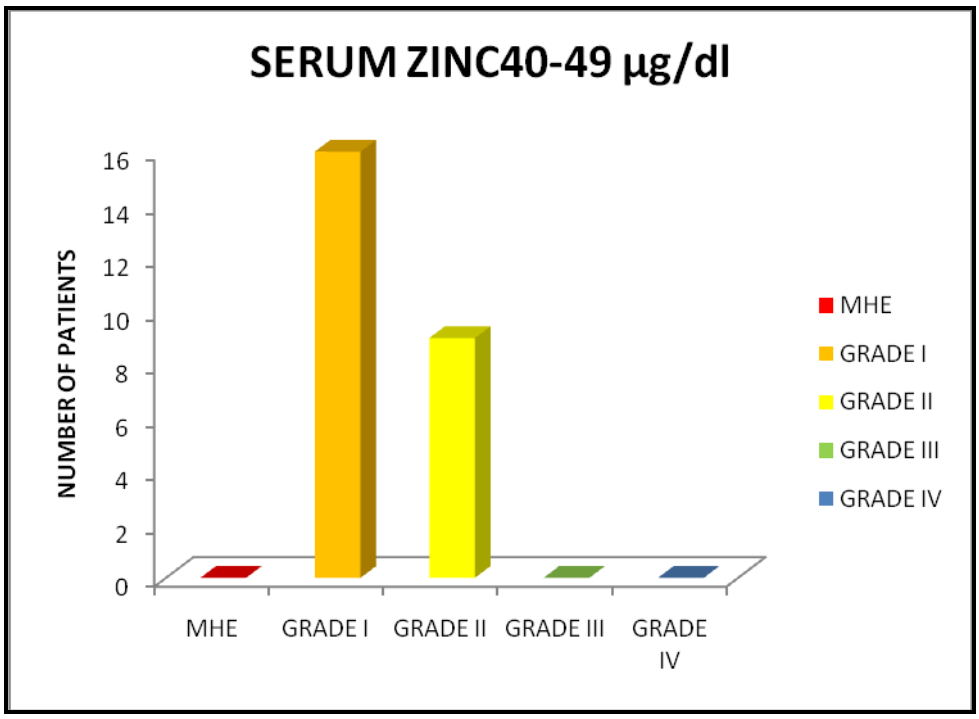

Figure: 11- Serum Zn level (40-49µg/dl) in patients with various grade of HE

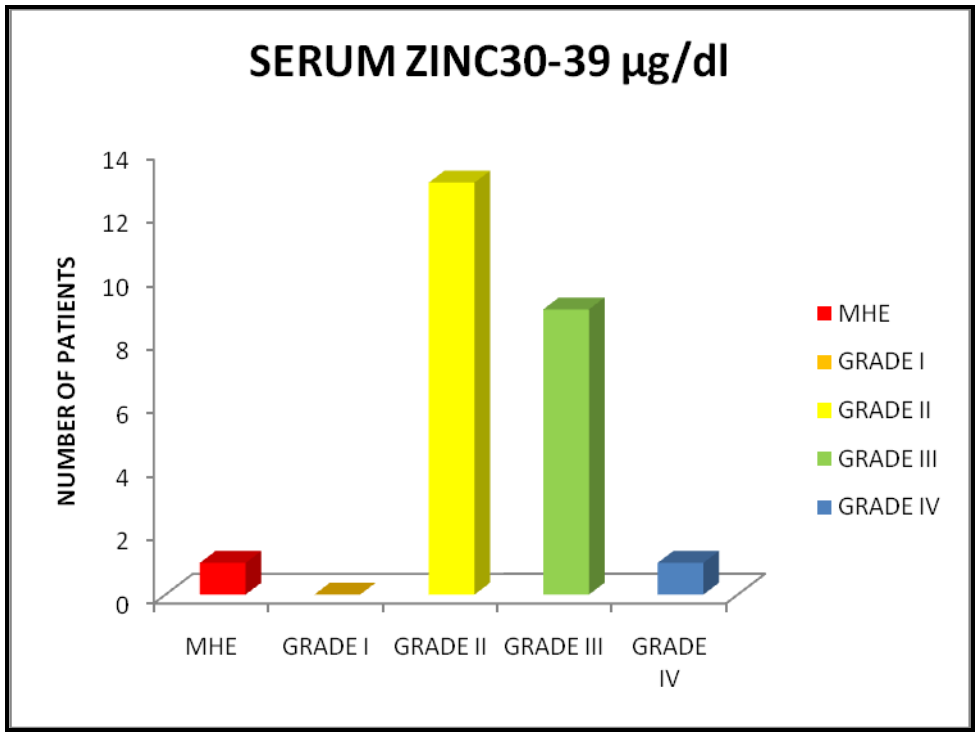

Figure: 12- Serum Zn level (30-39µg/dl) in patients presented with various grade of HE

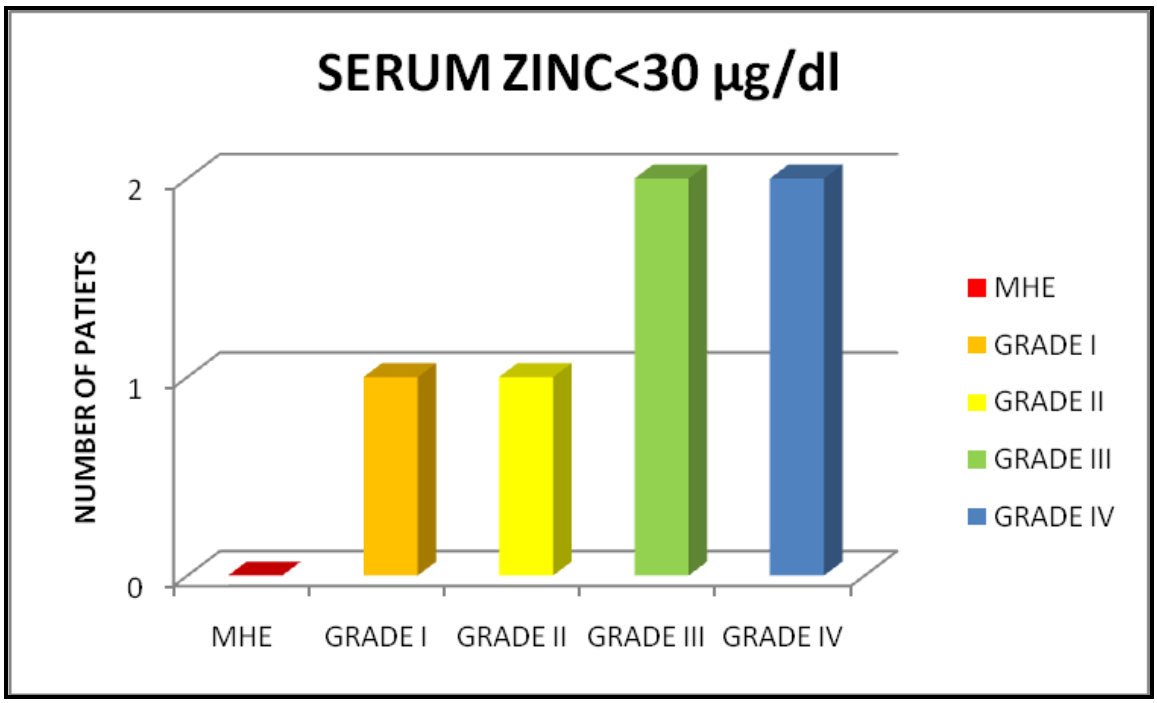

Figure: 13- Serum Zn level (<30µg/dl) in patients with various grade of HE

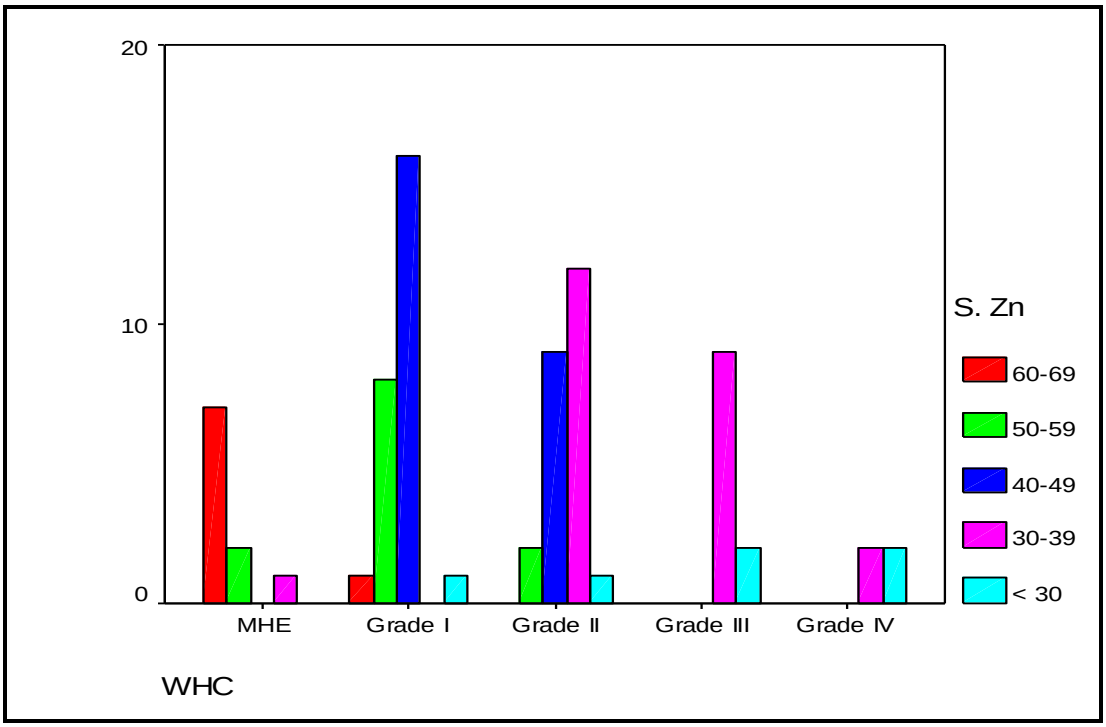

Figure: 14 –distribution of HE grade according serum Zn level

In our study statistically significantly association low zinc values and higher grades of hepatic encephalopathy (p-value 0.001)

SERUM ZINC LEVEL IN VARIOUS CHILD PUGH CLASS

Table10-Comparison of serum zinc level with Child pugh class

			S. Zn					Total
			60-69(I)	50-59(II)	40-49(III)	30-39(IV)	< 30(V)	
CPC	Class A	Count	6	2	1	0	0	9
		% within CPC	66.7%	22.2%	11.1%	.0%	.0%	100.0%
	Class B	Count	2	6	10	6	0	24
		% within CPC	8.3%	25.0%	41.7%	25.0%	.0%	100.0%
	Class C	Count	0	4	14	18	6	42
		% within CPC	.0%	9.5%	33.3%	42.9%	14.3%	100.0%
Total		Count	8	12	25	24	6	75
		% within CPC	10.7%	16.0%	33.3%	32.0%	8.0%	100.0%

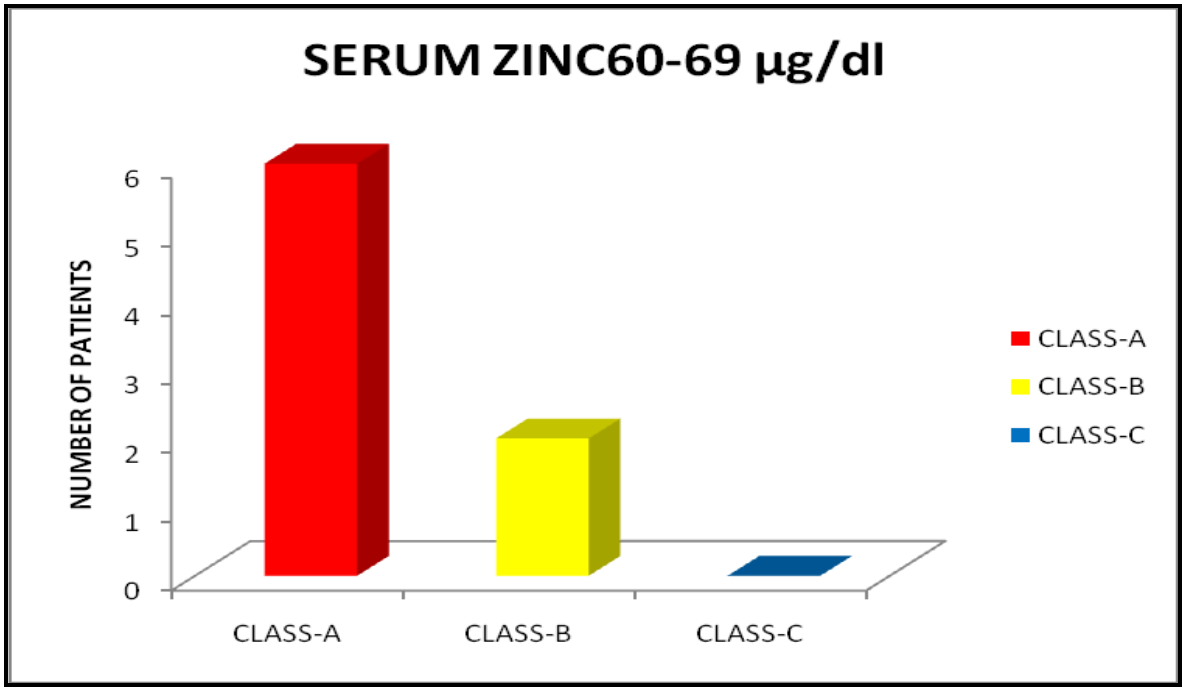

Figure15- Serum Zn level (60-69µg/dl) in patients with various child pugh classes

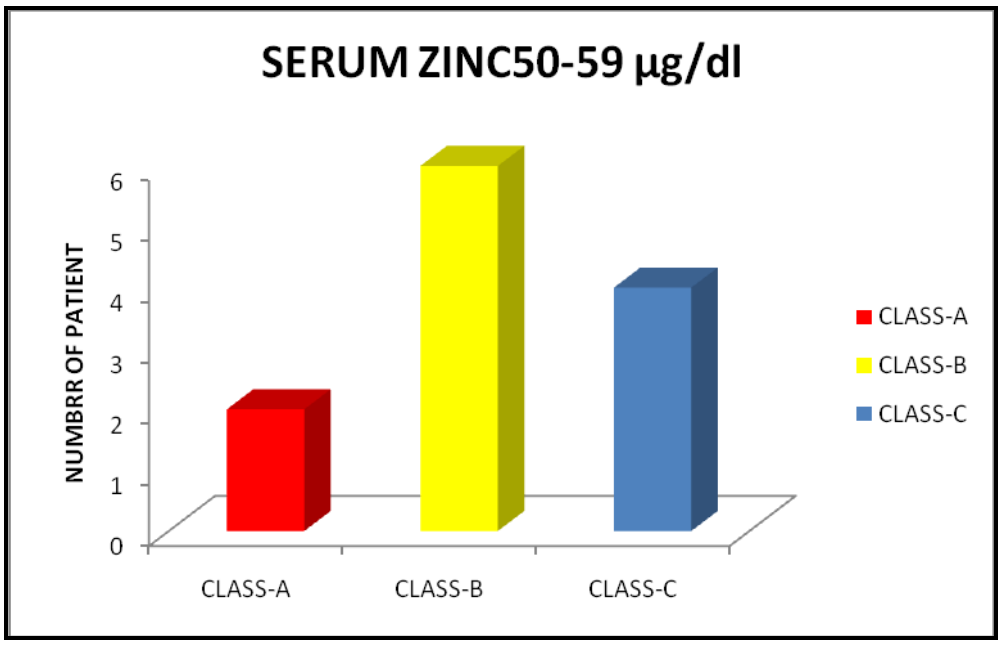

Figure16- Serum Zn level (50-59µg/dl) in patients with various child pugh

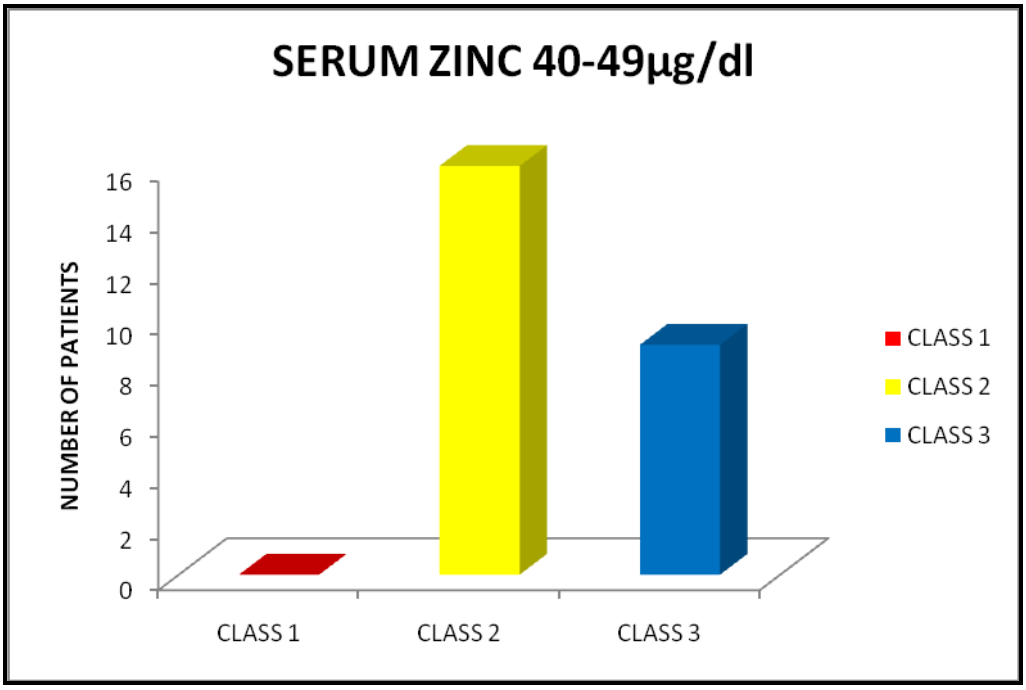

Figure17- Serum Zn level (40-49µg/dl) in patients with various child Pugh classes

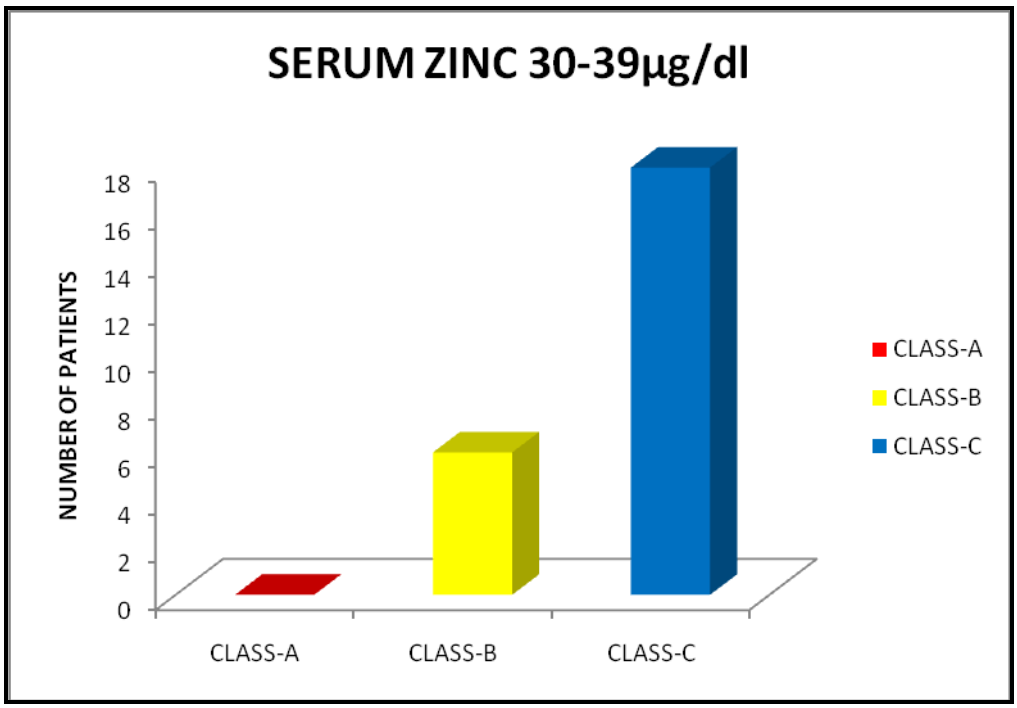

Figure18- Serum Zn level (30-39µg/dl) in patients with various child Pugh classes

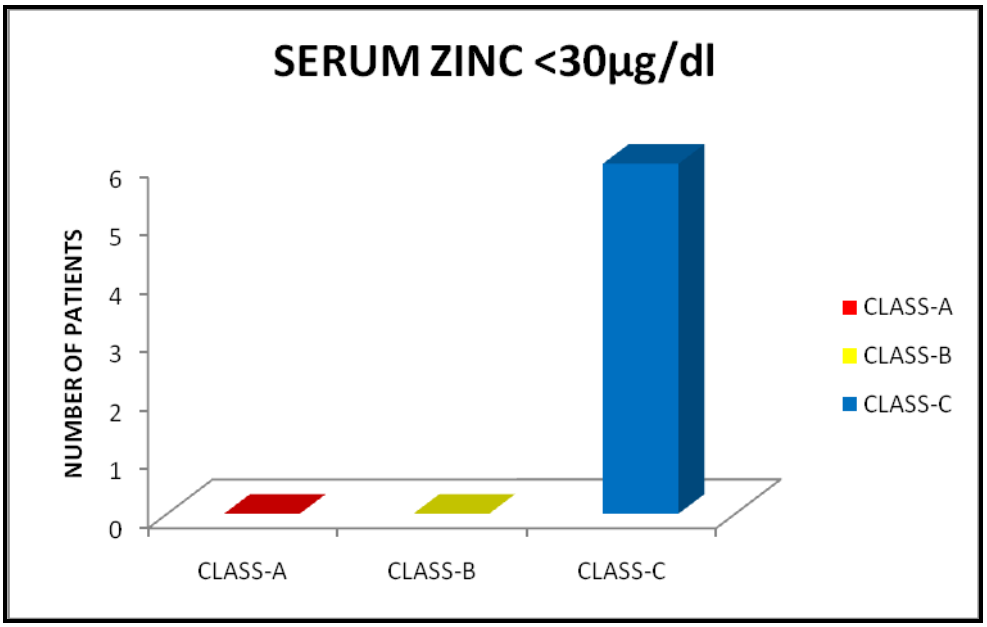

Figure19- Serum Zn level (<30µg/dl) in patients with various child Pugh

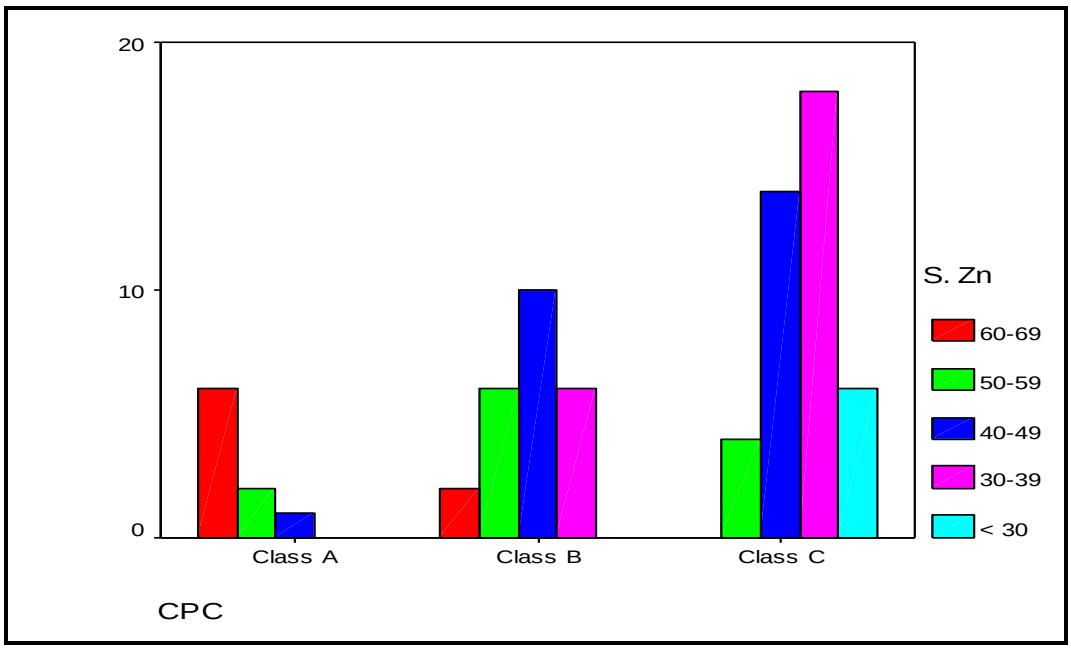

Figure20- Comparison of serum Zn level and Child Pugh score

In our study low serum Zn level have statistically significant association with higher child-Pugh score (p-value 0.001).

Table 11– Comparison between serum Zn level and serum Albumin level

			S. Zn					Total
			60-69	**50-59**	**40-49**	**30-39**	**< 30**	
SA	3.5-5.0 gm/l	Count	4	2	2	2	0	10
		% within SA	40.0%	20.0%	20.0%	20.0%	.0%	100.0%
	2.5-3.5 gm/l	Count	4	9	21	15	5	54
		% within SA	7.4%	16.7%	38.9%	27.8%	9.3%	100.0%
	< 2.5 gm/l	Count	0	1	2	7	1	11
		% within SA	.0%	9.1%	18.2%	63.6%	9.1%	100.0%
Total		Count	8	12	25	24	6	75
		% within SA	10.7%	16.0%	33.3%	32.0%	8.0%	100.0%

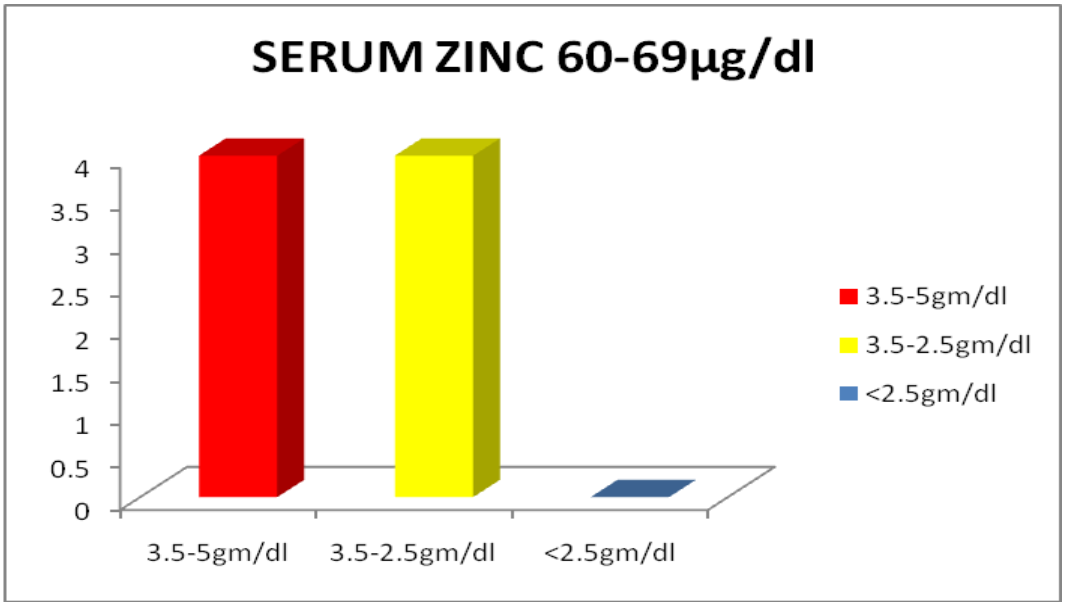

Figure21- Albumin level in patient with serum Zn (60-69µg/dl)

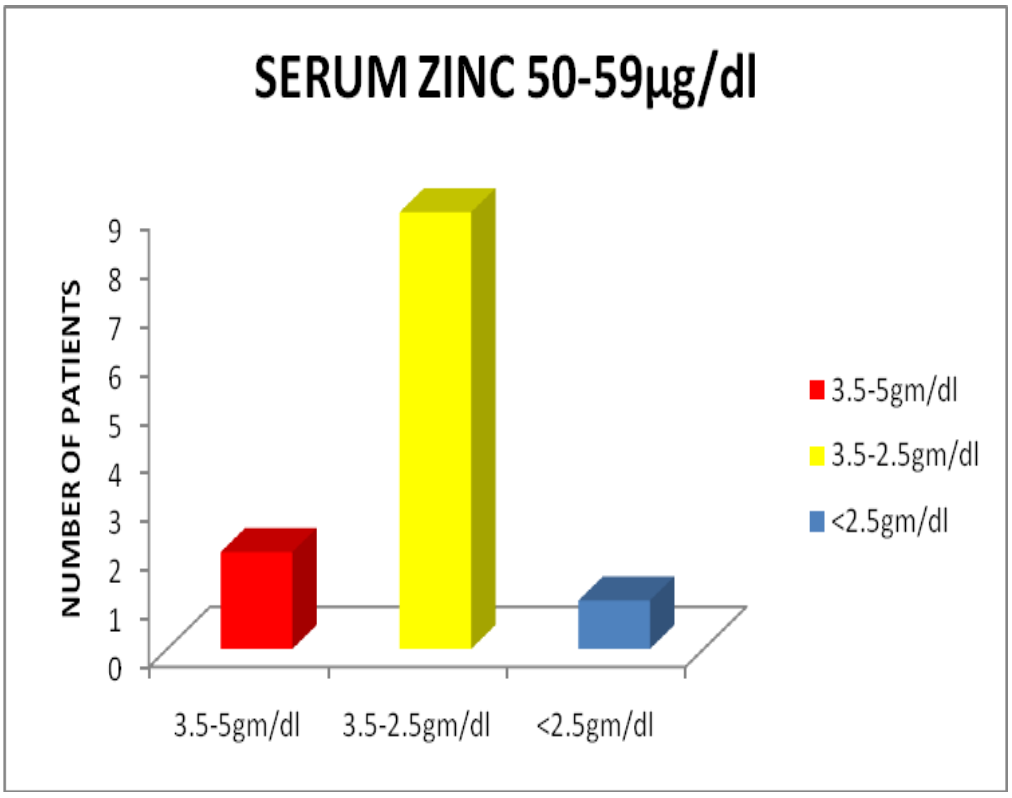

Figure22- Albumin level in patient with serum Zn (50-59µg/dl)

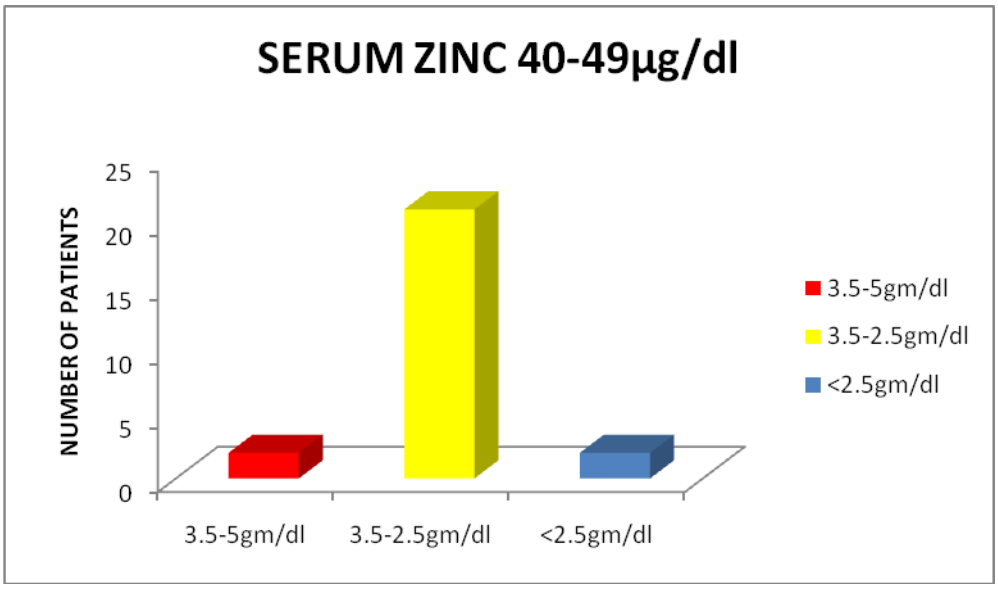

Figure23- Albumin level in patient with serum Zn (40-49µg/dl)

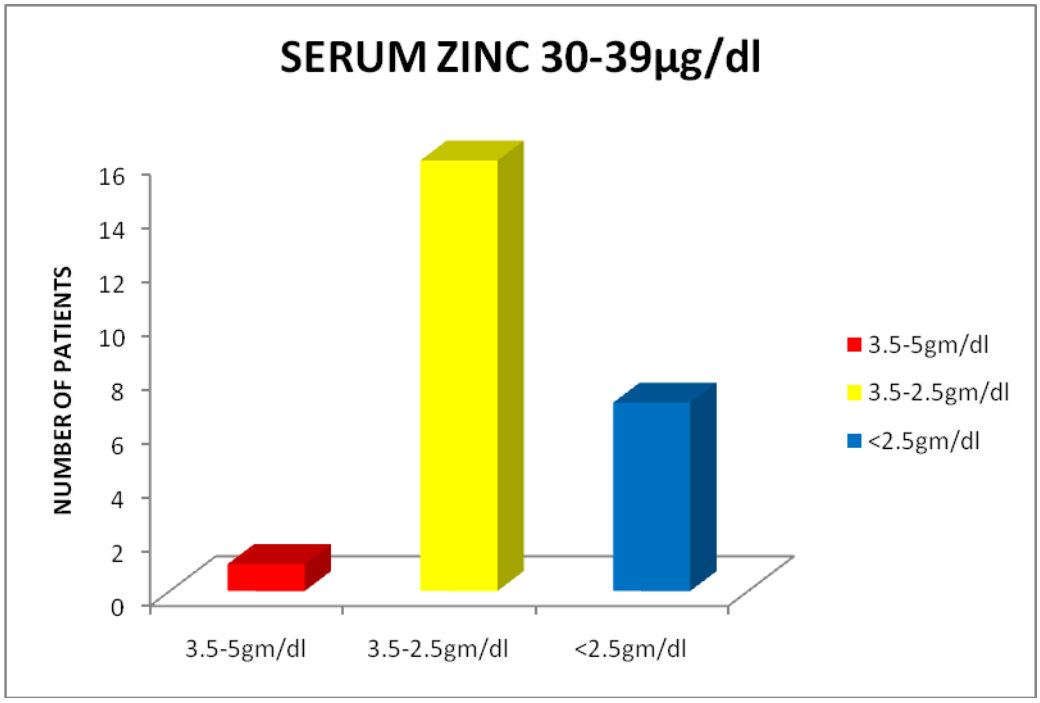

Figure24- Albumin level in patient with serum Zn (30-39µg/dl)

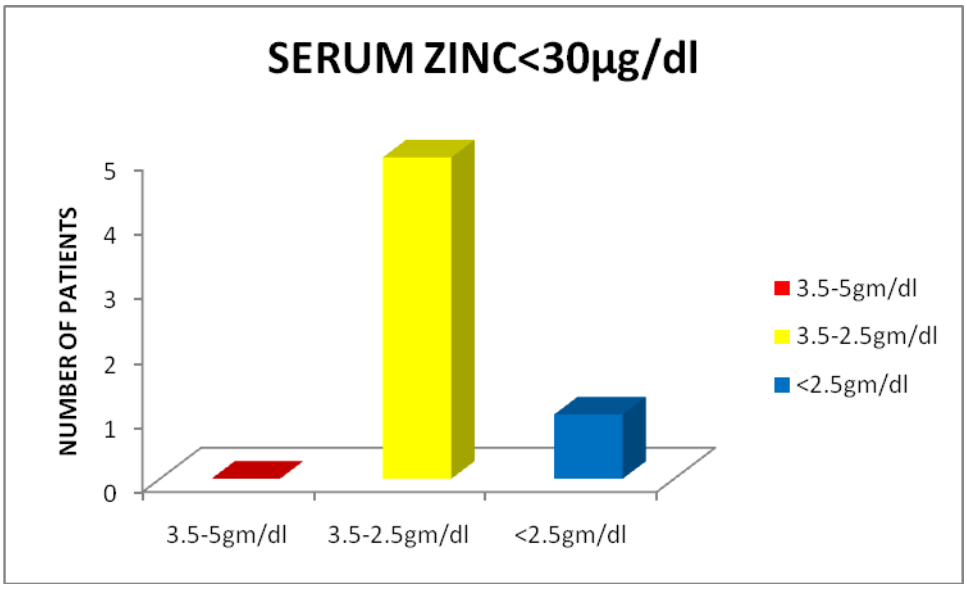

Figure25- Albumin level in patient with serum Zn (<30µg/dl)

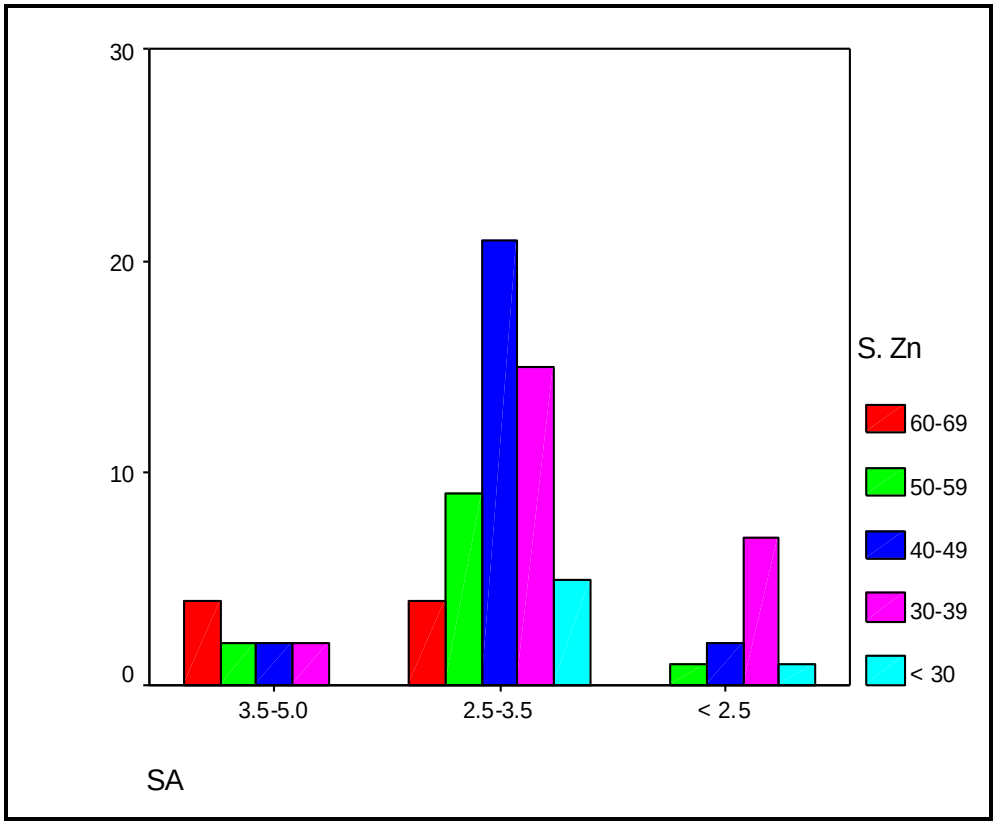

Figure26- Comparison between serum Zn level and serum Albumin level

In our study patients had low serum albumin statistically association with low level of serum Zn (p-value 0.029).

DISCUSSION

A cross sectional study done in 75 patients is diagnosed in DCLD with hepatic encephalopathy, conducted at Rajiv Gandhi Government General hospital Chennai.

Hepatic enc

302ephalopathy is one of the most serious and common complications in DCLD patient presented in hospital.(1)

In developing countries most common etiology in cirrhosis patients is viral hepatitis and second alcohol (1,2). In our study maximum cases develop cirrhosis due to Alcohol abuse (90% cases) and second viral hepatitis. [4,82]

In our study Male population more dominantly affected to DCLD with encephalopathy. [83]

Most commonly affected middle age group (19,81). In our study 63% cases were middle age between 30 to 50 year age group.

DCLD patients present as HE, majority of them identified clear precipitating factors. There are many factors have role in

precipitation in hepatic encephalopathy, common precipitating factors are constipation, infection and UGI bleeding. [81, 84]

UGI bleeding is most common factor according **Sheila Sherlock.**

Zinc level significantly low in DCLD [71], one study done by **Kaushik and** colleagues also same result.

Our study all DCLD patients admitted as complication HE ,had low serum zinc level. Patient who presented in worse grade HE, those found more drops in serum Zn that is clear in this study that low serum Zn significantly associated with high class of hepatic encephalopathy.

Zinc is important co-factor for many enzymes. Zn has key role in physiological detoxification of ammonia via urea cycle in liver and as a co factor in ornithine Transcarbamylase (OTC) so low zinc level associated with decreased OTC activity and higher plasma concentration of ammonia. low plasma Zn impairs nitrogen cycle in muscle and increase glutamine in blood. As result in advanced grade in HE significantly more drop in plasma Zinc (1). Short term oral Zinc supplement is very useful as an adjunct treatment in DCLD patient with hepatic encephalopathy[63].

In our study serum zinc level significantly low in higher grade of hepatic encephalopathy. Study done at **Egypt by Mohsen Maher** and collegue had similar result.

In this study, compression between serum Zn and stage of liver disease, Zinc level significantly low in worse class of cirrhosis,(4,71) in DCLD patient other factor like malnutrition, poor oral intake and diuretic use also related to low Zn level.

Serum Zinc (>80%) bound loosely with albumin, serum albumin concentration obviously decreased in DCLD patients. In our study low albumin level associated more drops in serum Zn. This study also indicates low serum Zn level may be contributed by significant low serum albumin concentration

LIMITATIONS OF STUDY

Further studies with adequate sample size and extended period are needed to confirm our study in DCLD patients with hepatic encephalopathy.

SUMMARY

- Hepatic encephalopathy is common and serious complication in DCLD patient admitted in hospital.
- Most common presenting complaint is acitis, other common are altered sleep pattern and disorientation.
- Common precipitating factors are constipation, infection and UGI bleeding.
- Male population predominantly affected.
- Common in middle age group (30-50 year)
- Alcohol abuse (>10 year duration) is common etiology in cirrhosis patients.
- All DCLD patient presented in HE had low serum Zinc level (<70 µg/dl), Zn deficiency significantly correlated with higher grade of HE.
- Patient who is in advanced class of DCLD had significant low Zn level most of patient in child class C had Zn level (30-39 µg/dl).
- Low albumin level in DCLD markedly associated with decrease plasma Zn level.

CONCLUSION

From this study all patients in DCLD with complication Hepatic encephalopathy identified low serum Zinc; it is associated with higher grade of HE.

More drops in serum Zn is correlated with worse grade of HE.

Low serum zinc is an indirect precipitating factor in HE.

Short term Zn supplement may be useful in prevention and treatment in HE patients.

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PROFORMA

SERUM ZINC LEVEL IN DECOMPENSATED LIVER DISEASE AND ITS CORRELATION WITH THE STAGE OF HEPATIC ENCEPHALOPATHY

Name: Patient IP No:

Age /Sex: Contact No:

PRESENTING SYMPTOM

Abdominal pain, Fever	Abdominal distension
Vomiting	Diarrhea
Constipation	Loss of appetite
Loss of weight	Jaundice
Fever	UGI bleeding
Urine out put	Leg swelling
Sleep pattern	Disorientation
Speech	Anxiety
Confusion	Coma
Fetor hepatics	

PAST HISTORY

Jaundice HT

DCLD DM

Other Neurological disease

PERSONAL HISTORY

Alcohol – amount and duration

Smoking

GENERAL EXAMINATION

Level of conscious:

Pallor:

Ictrus:

Pedal edema:

Clubbing:

Parotid enlargement:

Spider angioma:

Palmar erythema:

Acites :

Skin manifestations:

BP:

PR:

Weight:

Height:

SYSTEMIC EXAMINATION

Abdomen

Dilated vein

Distension

Organomegaly

CNS

Level of conscious

Number correction test (NTC)

Construction aprexia

GCS Score

Sleep pattern

Flapping Tremor

RS

CVS

INVESTIGATION

Total Bilirubin(mg/dl)

AST (IU/L)

APT (IU/L)

AP (IU/L)

Total Protein (gm/l)

Serum Albumin (gm/l)

Blood urea (mg/dl)

Serum creatinine (mg/dl)

Serum electrolytes (meq/l)

Serum Zinc

Total WBC count

Platelets count

Prothrombin Time

INR

Ultrasound abdomen

Portal Doppler

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. Rajesh Kumar Meena,
Post Graduate, MD (General Medicine)
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600003.

Dear Dr. Rajesh Kumar Meena,

The Institutional Ethics Committee has considered your request and approved your study titled **"SERUM ZINC LEVELS IN DECOMPENSATED LIVER DISEASE AND ITS CORRELATION WITH THE STAGE OF HEPATIC ENCEPHALOPATHY"** No. 57072014.

The following members of Ethics Committee were present in the meeting held on 01.07.2014 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 Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member Secretary
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

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

Sd/Chairman & Other Members

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

INFORMATION SHEET

We are conducting a study on "SERUM **ZINC LEVELS IN DECOMPENSATED LIVER DISEASE AND ITS CORRELATION WITH THE STAGE OF HEPATIC ENCEPHALOPATHY**" among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the correlation between serum Zinc level in Decopensated chronic liver disease, its complications and stage of hepatic encephalopathy. We are selecting certain cases and if you are found eligible, after filling up the questionnaire, 5 ml blood will be collected. You will also undergo clinical examination, serum Zinc, LFT, RFT and PT/APTT examination. These tests and special studies do not affect your final report or management.

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 | Signature of Participant

Date :
Place :

PATIENT CONSENT FORM

Study Title	:	Serum Zinc levels in Decompensated Liver disease and its correlation with the stage of Hepatic encephalopathy
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ☐

Signature/thumb impression
Patient's Name and Address:

Signature of Investigator
Study Investigator's Name:
Dr. RAJESH KUMAR MEENA

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனையில் திறனற்ற கல்லீரல் நோயாளிகளின் சீரம்சிங்க் அளவிற்கும் கல்லீரல் மூளை நலிவிற்கும் உள்ள தொடர்பினை பற்றிய ஆய்வாகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்களை எடுத்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

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

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

திறனற்ற கல்லீரல் நோயாளிகளின் சீரம்சிங்க் அளவிற்கும் கல்லீரல் மூளை நலிவிற்கும் உள்ள தொடர்பினை பற்றி ஆராய்தல்.

இந்த ஆராய்ச்சியில் திறனற்ற கல்லீரல் நோயாளிகளின் சீரம்சிங்க் அளவிற்கும் கல்லீரல் மூளை நலிவிற்கும் உள்ள தொடர்பினை பற்றி ஆராயப்படுகிறது. நீங்கள் தகுதியுள்ளவர் என்றால், உங்களின் முழு சம்மதத்தோடு, உங்களிடமிருந்து 5 மி.லி இரத்தம் எடுக்கப்படும். மேலும், உங்கள் இரத்தத்தில், கல்லீரல் செயல்பாடு மதிப்பீடு, சீறுநீரக செயல்பாட்டு மதிப்பீடு இரத்தம் உராய்தல் மதிப்பீடு ஆகியவற்றை செய்யப்படும் இந்த பரிசோதனைகள் உங்கள் சிகிச்சையை பாதிக்காது என்றும் உறுதி அளிக்கப்படுகிறது.

இந்த ஆராய்ச்சின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம்.

கையொப்பம்

KEY TO MASTER CHART;

Sex;
male-1

Female-2

Out come;
Recovered -1

Expired -2

Etiology of DCLD/HE;

Alcohol -1
HBV-2
HCV-3
Wilson disease-4
Other -5

Fever ;

Yes -1
No-2

Abdominal pain

Yes -1
No-2

Vomiting ;

Yes -1
No-2

Diarrhea ;

Yes-1
No-2

Constipation ;
Yes -1
No-2

abdomen distension
yes-1

no-2

UGI Bleeding;

Yes-1
no-1

Anorexia-
Yes-1
no-2

Malnutrition;
Yes-1
no-2

Ictrus-

yes -1
no-2

Pedal edema(PE)

yes -1

No-2

spider nevi;
Yes-1
no-2

palmar erythema ;

yes -1
no-2

parotid enlargement
yes-1
no-2

clubbing ;

yes -1
no-2

Spleen;

yes-1
no-2

liver;
yes-1
no-2

fector hepaticus ;
yes-1
no-2

construction aprexia
Yes-1
no-1

Sleep alteration
Yes-1

no-1

Asterixis ;
yes -1
no-2

Confusion ;

yes -1
no-2

Coma;
yes-1
no-2

West haven grading MHE-1	Clild –Pugh class classA-1	serum protein;
Grade-1-2	class B-2	decreased-1
Grade II -3	class C-3	normal(6.5-8)-1
Grade III -4		
Grade IV -5	AST	
Serum zinc(in microgm/dl)	elevated-1	serum albumin (3.5-5)
70-150 -1	normal-2	normal(3.5-5)-1
60-70-2		2.5-3.5=2
50-59-3	ALT-	less than 2.5=3
40-49-4	elevated-1	
30-39-5	normal-2	
Less than30-6		

Total bilirubin(mg/dl)	SAP	serum urea=
Less than2=1	elevated-1	elevated=1
2-5mg/dl=2	normal-2	normal=2
More than 5		

Serum creatinine(1.3	serum Na^+	Serum K(3.5-5)
Elevated=1	more than 150 meq/l-1	More than 5=1
Normal=2	normal135-150meq/l=2	normal(3.5-5)=2
	Less135meq/l=3	less 3.5meq/l=3

Total cell count ;
(Leucocytosis ≥11000;)

Yes -1

No-2

Platlets count ;
(Thrombocytopenia 1lakh)

Yes-1

No-2

PT/INR;(≥1.71)

Prolonged -1

Not-2

Age group-

≥50 year=1

30-50yr=2

≤30 year=3

Duration of alcohol intake

≥10 year=1

5-10year=2

≤5year=3

sl No	IPNo	Age[yr]	sex	outcome	Etio.	fever	abd pain	vomit	diarrhea	contip	abd dist	ugib	anorexia	malnutr	ictrus	PE	sp navei	palm ery	par en	club	spleen	liver	fet hep	BP
1	71804	47	1	1	1	1	1	2	2	1	1	1	1	2	1	1	2	2	1	2	1	2	2	2
2	71694	42	1	1	1	1	1	2	2	2	1	2	1	2	1	1	2	2	2	2	2	2	2	2
3	74478	60	1	2	1	1	2	1	2	1	1	2	1	1	1	1	2	2	1	1	1	2	1	1
4	74990	45	1	1	1	2	2	2	2	2	1	2	1	1	2	2	2	2	2	1	1	2	2	2
5	76681	35	1	1	1	1	1	2	1	2	1	1	1	2	1	1	2	2	2	1	2	2	1	2
6	76970	49	1	2	1	1	2	2	2	1	1	1	1	1	1	1	2	2	1	1	2	2	1	1
7	79734	69	1	2	1	1	1	2	2	1	1	1	1	1	1	1	1	1	2	2	1	2	1	1
8	79633	43	1	1	1	2	2	2	2	2	1	2	1	2	1	2	2	2	2	1	1	2	2	2
9	82074	43	1	1	1	1	1	2	2	1	1	1	1	2	1	1	1	1	2	1	1	1	1	2
10	82164	40	1	1	1	2	2	2	2	1	1	2	1	1	2	1	2	2	2	1	2	2	2	2
11	82238	38	1	1	1	1	1	1	2	2	1	1	1	1	1	1	2	2	2	2	2	2	2	1
12	82199	73	1	2	1	2	1	1	1	2	1	1	1	1	2	2	2	2	2	1	1	2	2	1
13	84684	46	1	1	1	2	2	2	2	1	1	1	1	2	1	1	2	2	1	1	1	2	2	2
14	84717	47	1	1	1	2	1	2	2	1	1	2	1	1	1	1	3	2	1	2	2	2	2	2
15	84723	65	1	1	1	2	2	2	1	2	1	2	1	1	2	1	2	2	2	1	1	1	2	2
16	84850	47	2	1	4	1	1	2	2	2	1	2	1	2	1	1	2	2	2	2	1	2	2	2
17	83507	67	1	1	1and2	2	1	2	2	1	1	2	1	1	1	2	2	2	2	2	1	2	1	2
18	83087	34	1	1	1	1	1	1	2	1	1	1	1	2	1	1	2	2	2	2	2	2	2	2
19	82206	47	1	1	1	1	1	2	2	1	1	1	1	2	1	1	2	2	2	2	2	2	2	2
20	84612	59	1	1	1	2	2	2	2	2	1	2	1	1	1	1	2	2	2	2	1	2	2	2
21	84110	38	1	1	1	1	2	2	2	2	1	2	1	2	1	1	2	2	2	2	2	1	2	2
22	84095	36	1	1	1and2	2	2	2	2	1	1	2	1	1	1	1	2	2	2	2	1	2	2	2
23	85385	53	1	1	1	2	2	2	2	2	1	1	1	1	1	1	2	2	2	1	1	2	1	2
24	86370	59	1	1	1	2	2	2	2	1	1	1	1	1	2	2	2	2	2	2	1	2	2	2
25	85358	55	1	1	1	2	1	2	2	1	1	2	1	1	2	2	2	2	1	1	1	2	2	2
26	84669	66	1	1	1	2	1	2	2	1	1	2	1	1	1	1	2	2	2	2	2	2	2	2
27	84828	52	1	1	1	2	2	2	2	1	1	1	1	2	1	1	2	2	1	1	1	2	1	2
28	84888	34	1	1	1	1	1	2	2	1	1	1	1	2	1	2	2	2	2	2	1	1	1	2
29	85183	68	1	1	1	2	2	2	2	1	1	2	1	1	1	1	2	2	2	1	1	1	2	2
30	85562	55	1	1	1	2	1	2	2	2	1	2	1	1	1	1	2	2	2	2	1	2	2	2
31	80334	32	1	1	1	2	2	1	2	2	1	1	1	2	1	2	2	2	1	2	1	1	2	2
32	84831	48	1	1	1	2	1	1	2	2	1	1	1	1	2	2	2	2	2	2	1	2	2	2
33	84311	58	1	1	1	1	1	2	1	2	1	1	1	1	2	2	2	1	1	1	2	2	2	2
34	84277	30	1	1	1	1	1	2	2	1	1	2	1	2	1	2	2	2	2	1	1	2	2	2
35	84135	49	1	1	1	2	2	2	2	1	2	1	1	1	1	1	2	2	2	1	2	2	1	2
36	82238	38	1	1	1	1	1	2	1	2	2	1	1	2	1	1	2	2	1	2	1	2	1	2
37	82199	73	1	1	1	2	1	2	2	1	1	2	1	1	1	1	2	2	2	1	2	2	1	2
38	82164	83	1	1	1	2	1	2	2	1	1	2	1	2	2	2	2	2	2	2	1	1	2	2

sl No	IPNo	Age[yr]	sex	outcome	Etio.	fever	abd pain	vomit	diarrhea	contip	abd dist	ugib	anorexia	malnutr	ictrus	PE	sp navei	palm ery	par en	club	spleen	liver	fet hep	BP
39	84975	50	2	1	2	1	1	2	2	1	1	2	1	1	1	2	2	2	2	2	2	1	2	2
40	85206	36	1	1	1	2	1	1	2	2	1	1	1	1	1	2	2	2	2	2	2	1	2	2
41	85890	52	1	1	1	2	1	1	1	2	1	2	1	1	1	2	2	2	2	1	2	2	2	2
42	83866	55	1	1	1	2	2	2	1	2	1	2	1	1	2	2	2	2	2	1	2	1	2	2
43	86022	56	1	1	1	2	1	2	2	1	1	1	1	2	1	1	2	2	1	1	1	2	1	2
44	86448	48	1	1	1	1	1	2	2	1	1	2	1	1	1	1	2	2	2	1	2	2	2	2
45	87015	47	1	1	1	1	1	2	2	1	1	2	1	1	1	1	2	2	2	2	2	1	2	2
46	87216	56	1	1	1	2	2	2	2	1	1	1	1	2	1	1	2	2	2	2	1	2	2	2
47	87255	49	1	1	1	2	2	2	2	1	1	2	1	1	1	1	2	2	2	2	1	2	1	2
48	87201	38	1	1	1	1	1	1	2	2	2	2	1	2	1	2	2	2	2	2	1	1	2	2
49	87271	49	1	1	1	2	2	2	2	1	1	1	1	1	1	2	2	2	2	1	1	2	1	2
50	87290	52	1	1	1	2	1	2	2	1	1	2	1	1	1	1	2	2	2	2	2	2	2	2
51	89771	48	1	1	1	2	2	2	2	1	1	2	1	1	1	1	2	2	2	2	2	2	2	2
52	90024	40	1	1	1	1	1	2	2	2	1	1	1	1	1	1	2	2	2	2	2	1	2	2
53	89187	50	1	1	1	1	2	2	2	1	1	2	1	1	1	1	2	2	2	1	1	2	2	2
54	88008	49	1	1	1	2	2	2	2	2	1	2	1	1	2	2	2	2	2	2	2	2	2	2
55	90472	46	1	1	2	1	1	2	2	2	1	2	1	2	1	2	2	2	2	1	1	1	2	2
56	91718	47	1	1	1	1	1	2	2	2	1	1	1	1	1	1	2	2	2	2	1	1	2	2
57	90551	62	1	1	1	2	2	1	2	2	1	1	1	2	1	2	2	2	2	2	1	2	2	2
58	89599	44	1	1	1	2	2	2	2	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2
59	89686	55	1	1	1	2	2	2	2	1	1	2	1	1	1	1	2	2	2	2	1	2	2	2
60	91507	51	1	1	1	2	1	1	2	2	1	1	1	1	1	2	2	2	2	2	1	2	2	2
61	90804	37	2	1	2	2	2	1	2	2	1	1	1	1	1	2	2	2	2	2	2	1	2	2
62	90271	45	1	2	1	1	1	2	2	1	1	2	1	1	2	1	2	2	2	2	1	2	1	2
63	90280	43	1	1	1	2	1	2	2	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2
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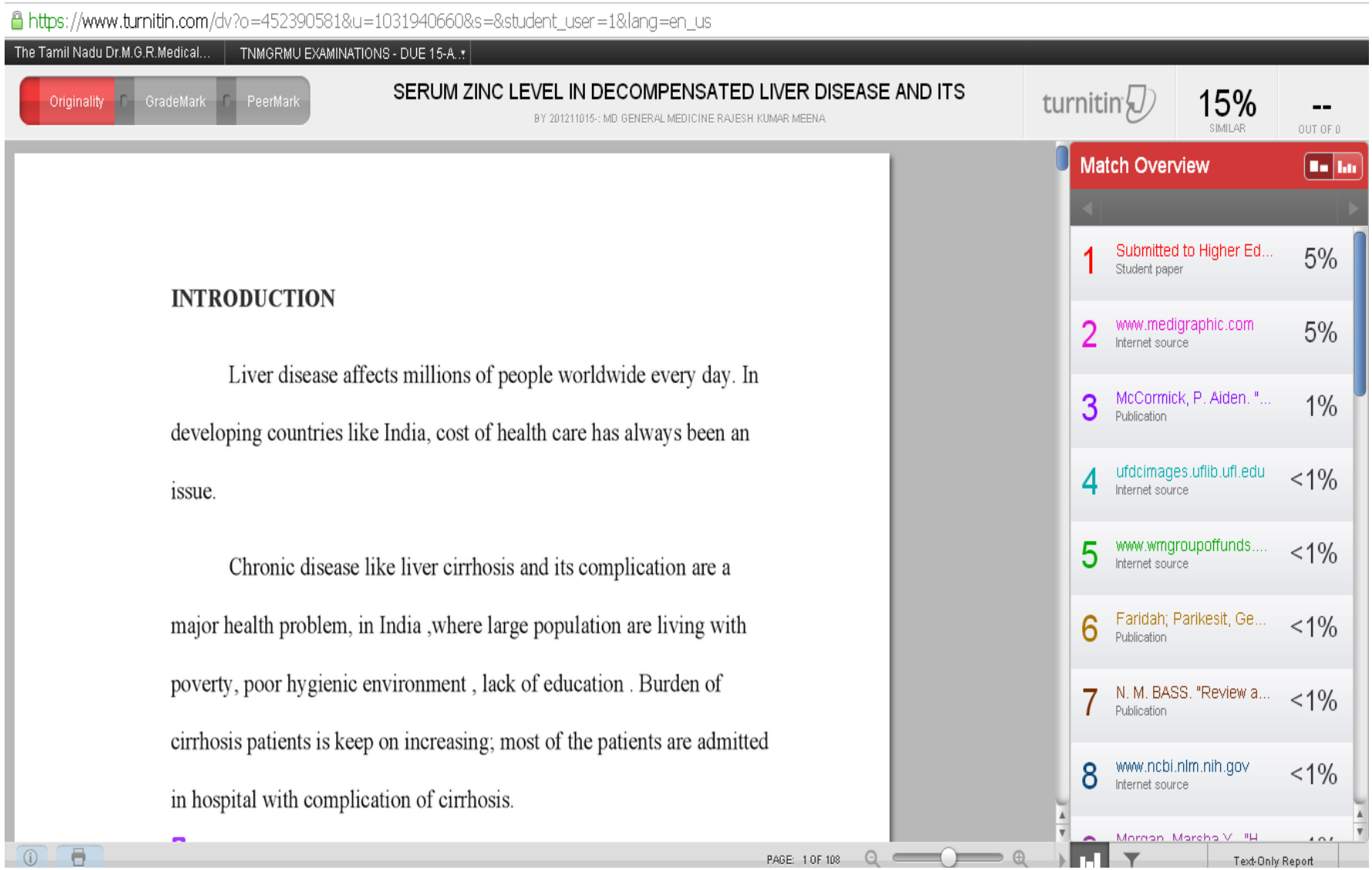
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INTRODUCTION
Liver disease affects millions of people worldwide every day. In developing countries like India, cost of health care has always been an issue.
Chronic disease like liver cirrhosis and its complication are a major health problem, in India ,where large population are living with poverty, poor hygienic environment , lack of education . Burden of cirrhosis patients is keep on increasing; most of the patients are admitted in hospital with complication of cirrhosis.
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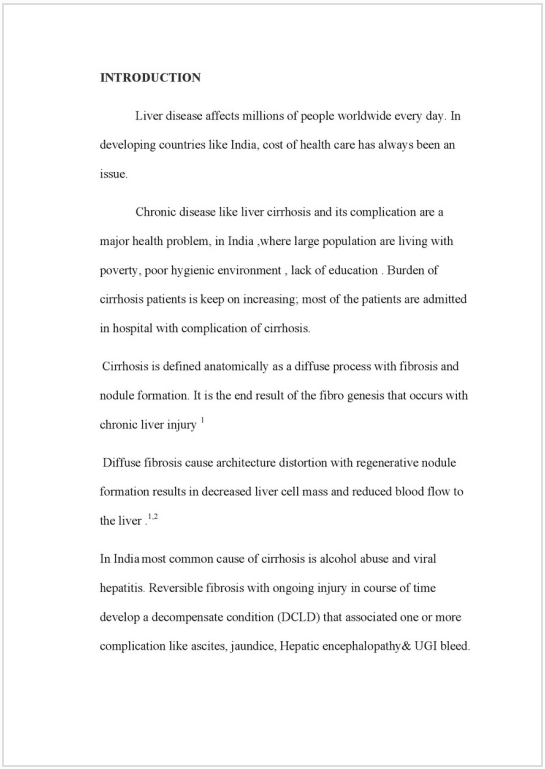

INTRODUCTION

Liver disease affects millions of people worldwide every day. In developing countries like India, cost of health care has always been an issue.

Chronic disease like liver cirrhosis and its complication are a major health problem, in India ,where large population are living with poverty, poor hygienic environment , lack of education . Burden of cirrhosis patients is keep on increasing; most of the patients are admitted in hospital with complication of cirrhosis.

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation. It is the end result of the fibro genesis that occurs with chronic liver injury [1]

Diffuse fibrosis cause architecture distortion with regenerative nodule formation results in decreased liver cell mass and reduced blood flow to the liver .[1,2]

In India most common cause of cirrhosis is alcohol abuse and viral hepatitis. Reversible fibrosis with ongoing injury in course of time develop a decompensate condition (DCLD) that associated one or more complication like ascites, jaundice, Hepatic encephalopathy& UGI bleed.

Table – comparison between Zn deficiency and WHC grade of HE

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	93.134(a)	16	.001
Likelihood Ratio	89.697	16	.001
Linear-by-Linear Association	42.311	1	.001
N of Valid Cases	75		

Table- comparison serum Zn with Child score

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	44.938(a)	8	0.001
Likelihood Ratio	40.301	8	.001
Linear-by-Linear Association	29.617	1	.001
N of Valid Cases	75		

Table- comparison of serum albumin with serum Zn

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	17.127(a)	8	.029
Likelihood Ratio	15.377	8	.052
Linear-by-Linear Association	9.772	1	.002
N of Valid Cases	75		