SPECTRUM OF PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER

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CERTIFICATE

This is to certify that the dissertation titled **"SPECTRUM OF PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER"** is the bonafide original work of **Dr. P. K. SIVA** in partial fulfillment of the requirements for **M.D. Branch – I (General Medicine)** Examination of the Tamil Nadu Dr. M.G.R Medical University to be held in MARCH 2009. The period of study was from June 2007 to June 2008.

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DECLARATION

I, Dr. P. K. SIVA hereby solemnly declare that the dissertation titled **"SPECTRUM OF PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER"** was done by me at Govt. Stanley Medical College and Hospital from June 2007 to June 2008 under the supervision and guidance of my Unit Chief and **Head of Department of Medicine Prof**.**V.RUCKMANI,M.D.,**

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INDEX

CONTENTS PAGE NO

INTRODUCTION

Liver diseases affect millions of people worldwide each day. However, in the developing countries where cost of health care has always been an issue, long lasting diseases such as liver cirrhosis and its complications are a major health problem and pose a big challenge to the health economy. Because of poverty, poor hygienic conditions, inadequate education and lack of counseling, the number of cirrhotic patients is increasing and most of them are admitted to medical wards with different complications.

The syndrome of hepatic encephalopathy(HE)[1] describes all neuropsychiatric symptoms occurring in patients with acute or chronic liver diseases (CLD) in the absence of other neurological disorders. About 30% of patients with cirrhosis die in hepatic coma[2]. Appearance of HE in any patient is indicative of poor prognosis[4]. HE can occur either due to acute liver failure or due to one or more precipitating factors in a cirrhotic patient, or it could happen as a result of prolonged portal systemic shunting resulting in a chronic portal systemic encephalopathy[5].

Survival of patients having chronic portal systemic encephalopathy is better than those who develop HE acutely (100% vs. 70%)[6]. However

prognosis in the later group can be improved if the precipitating factors are recognized early and managed accordingly[7].

Common precipitating factors include gastrointestinal bleeding , infection, azotemia, constipation, electrolyte imbalance[8] and high protein diet. Usage of drugs such as sedatives[9], tranquilizers, analgesics and diuretics, fulminant hepatic injury, large volume paracentesis have all been considered to precipitate encephalopathy in an otherwise stable cirrhotic patient.

Exact pathogenic mechanism involved is unknown till date, however the basic processes are failure of hepatic clearance of gut derived substances such as ammonia, free fatty acids, mercaptans etc., either through hepatocellular failure or shunting, and altered amino acid metabolism, both of which result in changes in cerebral transmission causing depressed cerebral function[10].

This study was aimed at ascertaining the common precipitating factors and their frequency in patients presenting with HE. Other objectives were to analyse the commonly associated biochemical laboratory findings in such patients, to stratify these patients according to Child's classification of CLD, the outcome, and the etiological factors involved.

AIM OF THE STUDY

This study was carried out with the main objective of ascertaining the most common precipitating factor and their frequency in a group of patients presenting with hepatic encephalopathy in diagnosed cases of cirrhosis of liver of any etiology

REVIEW OF LITERATURE

CIRRHOSIS OF LIVER

GENERAL CONSIDERATION

Cirrhosis is diffuse septal fibrosis of the liver, associated with regenerative parenchymal nodules and a disturbed intrahepatic circulation. Fibrous sheets link portal tract, central zones and portal tracts and central zones. Cirrhosis results from prolonged, widespread but patchy hepato-cellular necrosis due to various reason.

The most important classification of cirrhosis is based on etiology. The most common and important causes are prolonged Alcoholic liver disease and chronic hepatitis infection with Hepatitis B & C viruses.

The less important causes Hemochromatosis, α 1 anti trypsin deficiency, Wilson's disease, Cystic fibrosis, Glycogen storage disease, Galactosemia, Hereditary fructose intolerance.

The potentially treatable causes for cirrhosis being wilson's disease, Budd Chiari Syndrome, Veno Occlusive Disease, Hepatitis C infection. These disease should be diagnosed as early as possible

CAUSES FOR CIRRHOSIS

Alcohol

Chronic Viral Infection

Drugs and Toxins

Autoimmune Chronic Liver Disease

METABOLIC CAUSES

Hemochromotosis

A 1 Antitrypsin Deficiency

Wilson's disease

Cystic Fibrosis

Glycogen Storage Disease

Galactosemia

Hereditary Fructose Intolerance

BILIARY TRACT DISEASE

Extra hepatic biliary obstruction

Intra hepatic biliary obstruction

Primary biliary cirrhosis

VENOUS OBSTUCTION

Veno occlusive disease

Budd chiari syndrome

Cardiac failure

EPIDEMIOLOGY

Chronic liver disease and cirrhosis results in 26000-35000 deaths each year in india. Many patient die from the disease in the fifth or sixth decade of the life. Each year 2000 additional deaths are attributed to Fulminant Hepatic Failure(FHF). FHF may be caused by viral hepatitis(A&B), Drugs(e.g acetaminophen), autoimmune hepatitis, Wilson's disease and a variety of less common etiologies. Cryptogenic causes are responsible for one third of fulminant cases. Patient with the syndrome of FHF have a 50-80% mortality unless they are salvaged by liver transplantation

Etiology

Alcoholic liver disease is still the predominant cause of cirrhosis in india, with chronic hepatitis B & C close second.

Most common cause of cirrhosis in india

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

The term compensated and decompensated cirrhosis is often used. A patient with compensated cirrhosis has no problem with regard to cirrhosis while a patient with decompensated cirrhosis either have signs of liver cell failure or complication of cirrhosis.

PATHOPHYSIOLOGY OF HEPATIC CIRRHOSIS

The development of hepatic cirrhosis reflect a alteration in the normally balanced processes of extracellular matrix production and degradation. Extracellular matrix the normal scaffolding for cells hepatocytes is composed of collagens (especially type 1,III,V), glycoproteins, proteoglycans. Stellate cells, located in the peri-sinusoidal are essential for the production of extracellular matrix. Stellate cells which were once known as Ito cells, lipocytes or peri-sinusoidal cells may become activated into collagen forming cells by variety of paracrine factors. Such factors are released by hepatocytes, kupffers cell and sinusoidal endothelium following liver injury. As an example increase levels of cytokine transforming growth factor β 1 is observed in patients with chronic hepatitis C and those with cirrhosis. TGF β 1 in turn stimulate stellate cells to produce type 1 collagen. Increased collagen deposition in the space of Disse (the space between hepatocytes and sinusoids) and the

diminution of the size of endothelial fenestrae lead to the capillarisation of sinusoids. Activated stellate cells also have contractile properties. Both capillarisation and constriction of the sinusoids by the stellate cells contribute to the development of portal hypertension. Future drug strategies to prevent fibrosis should focus on reducing hepatic inflammation, inhibiting stellate cell activation, inhibiting the fibrogenic activities of stellate cell and degradation of matrix.

HISTOLOGY :

The main histological feature are diffuse septal fibrosis and regenerative nodules. With micro nodular cirrhosis which is usually obvious in needle Biopsy Specimen the nodules are uniformly small and similar in size to liver lobules.

In micronodular cirrhosis the nodules are variable in size and may be more than 10 mm. It may not be visible on nodule biopsy as complete nodule formation may not be evident. Other histological features, such as fragmentation and pattern of fibrosis especially on reticular staining may suggest the correct diagnosis. Silver staining may be required to bring out the early cirrhosis. Cell necrosis, evidence of active regeneration and cellular infiltrate indicate that the etiological agent is still alive. The nature of that agent may be evident on histological examination.

On taking the biopsy from the histological specimen care should be taken to take the biopsy from the nodules visible on ultra sound examination. Open biopsy by laproscopic examination often yields better results. Endoscopic guided biopsy is also under development

CLINICAL FEATURES

Cirrhosis can present without symptoms or signs and may be found incidentally. Clues to the presence of cirrhosis and its etiology usually comes from history.

Symptoms

Jaundice is usually absent in cirrhosis. It suggest either the causative agent is still active, that there is reason for decompensation, or a drug might have caused further impairment.

Weakness, easy fatigueagability, tiredness are very common and contribute to the general malaise of cirrhosis though objective evidence of weakness is unusual. Anorexia is frequently present. When present it is an ominous sign. Weight loss is seen in end stage cirrhosis.

Nausea and Vomiting are common. A remediable cause should be sought first. Vomitus should be examined to rule out haematemesis.

Abdominal pain or discomfort is common, usually in the right upper quadrant or right lower ribs. Generalized discomfort may occur with abdominal distention due to ascites and related to the rate of fluid accumulation and tension in the abdominal wall.

Increased stool frequency or constipation, both may occur in cirrhotics. Fluid retention leads to ankles and legs. Pruritis is a important presenting feature in primary biliary cirrhosis

Dyspnoea may be associated with gross ascites. In patient with some type of cirrhosis it is associated with fibrosing alveolitis, pulmonary shunting, pulmonary hypertension

Patient with cirrhosis develop spontaneous bleeding from the nose or gums. Cirrhotic may develop hepatic encephalopathy. Fever is common may have no obvious cause. Depression is common.

PHYSICAL SIGNS

Most patients with cirrhosis look well until the late stage of their disease, when muscle wasting and loss of adipose tissue may become prominent. An acute worsening of appearance should suggest infection or bleeding, while more prolonged deterioration results from decompensation.

Pallor may be due to recent UGI bleed or iron deficiency anemia due to chronic blood loss. Overt jaundice suggest hepatic decompensation and usually a ominous sign.

Cyanosis is uncommon except there is marked pulmonary shunting. Mild shunting is common in cirrhotics. Hypertrophic ostoearthropathy may also be present. Spider naevi, Palmar erythema, Paper money skin etc are found in cirrhosis especially alcoholic cirrhosis. Excessive bruising and petechiae are noted when liver function deteriorates.

Many cirrhotics especially those with hemochromatosis show widespread melanin pigmentation with local area of hyperpigmentation. Vitiligo appear in autoimmune liver disease. Lichen planus is associated with primary biliary cirrhosis

Gynaecomastia and testicular atrophy are common in cirrhosis especially alcoholic cirrhosis or hemochromatosis and is usually associated with thinning of hairs and signs of feminization

Dupuytren's contracture and Parotid enlargement are seen more common in alcoholic cirrhosis. They are more related to alcoholism than to cirrhosis

Flapping tremors or asterixis may be observed in patient with hepatic encephalopathy. Kayser- Fleischer ring is a particular valuable sign to look for in the case of Wilson's disease as it is a potentially treatable condition.

ABDOMINAL SIGN

Abdomen may distended due to accumulation of fluid or enlargement of abdominal organs. Skin over the abdomen may appear dry with prominent dilated veins. Multiple dilated veins may be seen.

Ascites is commonly seen in decompensated cirrhosis. The abdomen appears distended and the umbilicus is everted. Shifting dullness is present.

Dilated veins may be seen over the abdominal wall peri-umbilically (caput medusa) or over the flanks(Budd Chiari)

Enlarged liver or spleen can give rise to local bulging of the abdomen. The firm cirrhotic liver may be normal, palpable in the early stages shrunken in late stages with nodularity.

Measurement of the liver span is helpful in diagnosis of shrunken liver. The normal range is 12-16 cm by western statistics. According to Indian

statistics it ranges from 9-14 cm. A shrunken liver is better appreciated by ultrasound. Percussion of the abdomen is helpful in diagnosis of ascites

Auscultation may reveal a bruit of the liver (Hepatoma) or a venous hum in the epigastrium (portal Hypertension), a friction rub over the liver (tumour) or over the spleen (infarction). A continuous venous hum may be auscultable over the epigastrium (Bomgarten Phenomenon).

In the case of presence of enlarged veins the direction of flow should be determined. The presence of the veins and their exact location should be plotted. The presence or absence of pedal edema is also significant importance in distinguishing between veno-occlusive disease and Budd Chiari syndrome

INVESTIGATION:

HAEMATOLOGY

Routine haematological values may be normal in all cirrhotics. Mild anaemia is common. On blood films target cells may be seen and in rare cases acanthocytes and other features of haemolysis may be seen.

The White Cell count tends to fall in patient with cirrhosis, due to hypersplenism. If the white cell count is raised an infection should be sought for carefully. The platelet count is usually low in the cirrhotics due to hypersplenism. Coagulation factor are diminished due to hepatocellular damage. Factors 2, 7, 9,10 are affected more out of which factor 7 is the most affected. And earliest changes occur in factor 7 concentration. Prothrombin time is prolonged in decompensated cirrhotics.

BIOCHEMICAL

LIVER FUNCTION TEST

They are of limited value in cirrhosis, as they may be normal. AST and ALT

are normal in cirrhosis if causative agent is no longer active or with effective therapy,(ex Interferon, Ribavarine). In alcoholic cirrhosis the AST/ALT ratio is usually greater than 2. In most patients serum alkaline phosphatate is normal except in biliary cirrhosis

The gamma glutamyl transferase level may be increased in alcoholic cirrhosis. The serum total bilirubin level is usually normal. But bilirubin may be increased in states of increased bilirubin load like haemolysis, UGI bleed, certain drugs like steroids. An increased in bilirubin without any obvious cause suggest hepatic decompensation.

Low albumin levels are usually due to reduce hepatic synthesis. However it is also due to extracellular volume expansion or due to GI or renal causes.

OTHER BIOCHEMICAL TESTS

Plasma electrolytes are usually abnormally in cirrhosis and requires close monitoring.

Hyponatremia is common usually due to excess water intake or due to preferential salt loss due to diuretic therapy. Hypernatremia is less common and may occur with GI bleed, use of lactulose, and with severe fluid restriction.

Serum potassium is usually normal in cirrhotics. But both hyper and hypo kalemia is observed depending upon he type of diuretic instituted. Ex spironolactone produces hyperkalemia, While furesemide produces hypokalemia. Urine sodium and potassium measurement are useful to guide diuretic therapy. The dose of spironolactone should be increased till the urine sodium/potassium ratio is grater than 1.

Hypomagnesemia and Hypophosphatemia is also common in alcoholic patient with cirrhosis. The electrolyte abnormality should be diagnosed and treated as early as possible.

In well compensated cirrhosis, the urea level is normal but it falls short once decompensation occur due to inadequate hepatic production. So renal failure in cirrhosis should be monitored by serum creatinine. Renal failure is common in cirrhosis is common due to hypotension, diuretics, hepatorenal syndrome etc

Fasting blood glucose is usually normal, but most of the cirrhosis are insulin resistant and have post prandial hyperglycemia.

The serum cholesterol is normal in cirrhotics. In end stage cirrhosis the levels of lecithin cholesterol Acyl transferase falls and cholesterol ester

levels falls, while free cholesterol level increase. Cholesterol levels are raised in cases of biliary cirrhosis often to very high levels.

Anti mitochondrial antibody are raised in primary biliary cirrhosis. The test is relatively significant for diagnosing primary biliary cirrhosis.

Anti-smooth muscle antibody and anti LKM antibody are found elevated in auto immune hepatitis. Cryoglobulins and gamma globulin levels are also found elevated in many cases of cirrhosis due to the more frequent incidence of subclinical septecemia

ANATOMICAL AND PATHOLOGICAL DIAGNOSIS

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

THIS MAY BE DONE BY:

1. **Laproscopy:** Visualizes the liver and enables direct biopsy.
2. **Ultrasound:** is suggested by dense reflective areas of irregular distribution and increased echogenicity. However ultrasound is not reliable for diagnosis unless ascites is present.

3. **CT Scan**: Liver size can be assessed and the irregular nodular surface seen. Portal and hepatic vessels can be imagined with contrast. Ascites can be seen and gall stone can be visualized.
4. **Biopsy:** Reticulin and collagen stains are essential to highlight the fibrosis. Variability of liver cell size and presence of nodules with fibrous septa help in diagnosis.
5. **Radio Isotope Scanning**: in experimental stages

INVESTIGATION FOR ETIOLOGICAL DIAGNOSIS

It is important to establish the cause of cirrhosis

The following investigation are useful

1. Viral Serology:
   - HBsAg
   - IgM AND IgG anti HBV Antibody
   - IgM AND IgG anti HCV antibody
   - HCV RNA TITER
   - Liver biopsy
2. Serum Iron and Hepatic Iron content to rule out hemochromatosis
3. KF ring by slit lamp, serum and urinary copper to rule out Wilson's disease
4. Anti-mitochondrial Antibody
5. Anti Smooth Muscle Antibody
6. Anti LKM Antibody

7. **α –** Fetoprotein to rule out malignancy

Complication of cirrhosis

Major complication

1. Portal hypertension and ascites:

These are two of the major complication of cirrhosis but these can be caused by non cirrhotic portal fibrosis or extra hepatic portal vein thrombosis.

2. Hepatic Encephalopathy:

Major cause of cerebral disturbance and coma in cirrhotics. Encephalopathy can be caused by other process also.

3 Hepatocellular carcinoma:

One of the most serious complication of long standing cirrhosis also had a poor prognosis

4.Infection:

Important cause for sudden deterioration

MINOR COMPLICATION:

- Fluid & electrolyte disturbance
- Anaemia & Haemolysis
- Hepatorenal Syndrome
- Hepatopulmonary Syndrome
- Gallstones

PROGNOSTIC INDICATORS:

Child-Turcot-Pugh classification:

Class A 5-6 points

Class B 7-9 points

Class C 10-15 points

The higher the grade, the worse the prognosis

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 Seconds prolonged or INR	< 4 seconds or INR <1.7	4 seconds or INR 1.7-2.3	> 6 seconds or INR> 2.3
Ascites	none	slight	moderate to severe

2.**COX REGRESSION MODEL**

Poor prognosis is associated with:

- Prolonged Prothrombin Time
- Marked Ascites
- Gastrointestinal Bleeding

- Advanced Age
- Continuing Alcohol Consumption
- High Serum Bilirubin
- Spontaneous Bacterial Peritonitis
- Ascites

TREATMENT:

The management of well compensated cirrhosis is directed towards early detection of hepatocellular failure. An adequate balanced diet and abstinence from alcohol are essential.

A diet of 1 g of protein per kg of body weight is usually adequate. Hepato-protectives are useless. Additional branched chain amino acids are of no use. Onset of hepatocellular failure with edema warrants sodium restriction, diuretics, etc. Specific treatments to prevent complication should be instituted.

ANTIFIBROTIC THERAPY

1. Colchicine: Microtubule inhibitor, it's a relative harmless drug, only complication being diarrhea, and some efficacy in preventing progression of cirrhosis.
2. Steroids: Useful in autoimmune hepatitis. Otherwise has no role in therapeutics of alcohol cirrhosis.

3. Gamma interferon: Efficacy in cirrhosis not proven. Useful in treatment of acute and chronic hepatitis

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a potentially reversible, or progressive, neuropsychiatric syndrome characterized by changes in cognitive function, behavior, and personality, as well as by transient neurological symptoms and characteristic electroencephalographic patterns associated with acute and chronic live failure. Hepatic encephalopathy is a frequent complication of cirrhosis that is usually observed in association with severe hepatic insufficiency[30]. The characteristic presentation is the development of acute encephalopathy with an abrupt decline in the level of consciousness, manifested as confusion or coma. Frequently, a precipitating factors is identified. The treatment of the episode is directed toward the correction of the precipitating factor. Once the precipitating condition is resolved the encephalopathy also typically disappears, with the patient recovering to his or her previous state. However, in patients with low reserves of hepatic function, the hepatic encephalopathy can be a chronic condition. The low reserve predisposes the patient to development of spontaneous hepatic encephalopathy. There is usually a

precipitating factor, and the diagnosis and treatment should consider such aspects.

Chronic encephalopathy can manifest as frequent episodes of acute encephalopathy (chronic-recurrent encephalopathy)or with persistent neurological manifestations prominence of neurological manifestations. In practice, the distinction can be difficult because acute episodes coexist with the(chronic-persistent encephalopathy). The distinction between the two forms is subjective and is reflected in the chronic manifestations; if the manifestations are mild, the term “recurrent encephalopathy” should be used. On the other hand, if the chronic manifestations are severe, the term “persistent encephalopathy” is appropriate. In patients with chronic-recurrent encephalopathy, episodes can be associated with a precipitant factor but generally are spontaneous or related to the termination of treatment. It is not infrequent that these episodes are attributed to constipation, associated with administration of an in appropriate dose of non-absorbable disaccharide. An acute episode of spontaneous encephalopathy usually has an abrupt onset and termination. Between episodes, the patient can be alert and not display signs of cognitive dysfunction, unless he or she is examined by neuropsychological Testing[31]. Not infrequently, the patients present with a mild Parkinsonism, characterized by bradykinesia without tremor. Since hepatic encephalopathy is a viable option, since to a lesser extent patients

can also be treated with surgical portal-systemic shunts, chronic-persistent encephalopathy is less frequent than the recurrent form. The characteristic manifestations of recurrent encephalopathy are the development of dementia, severe Parkinsonism or myelopathy that can be associated with other neurological manifestations (ataxia, dysarthria, and tremor)[32]. In these patients, the cognitive alterations have a sub-cortical pattern: attention deficits, alterations in vision and practice, and the apraxia predominate. Most of the time these effects are transient, while bradykinesia and symmetric

rigidity predominate. Hepatic myelopathy presents as a spastic paraparesis with signs of a pyramidal involvement, but the senses are rarely affected[33].

PATHOGENESIS

For many years, controversy has existed about the origin of the toxins responsible for the altered mental state. There has been debate about the role of ammonium, synergic toxins, GABA or endogenous benzodiazepines in the development of hepatic encephalopathy. Today, it has been established that there are peripheral multi-organic alterations, as well as alterations in the intercellular communication of the brain, produced by alterations in astrocytes.

Peripheral alterations

a. *Intestinal*

There is controversy about the role of *Helicobacter pylori*, which produces ammonium in the stomach, in the pathogenesis of hepatic encephalopathy. Some trial shave demonstrated a high prevalence of the infection in individuals with alcoholic hepatitis who develop hepatic encephalopathy, as well as individuals with cirrhosis and chronic encephalopathy. However, eradication of *H. pylori* does not interfere with the levels of ammonium in this group of patients, and its contribution to the development of hepatic encephalopathy may therefore be minimal.

b. *Portal-systemic communication*

It has been demonstrated that some congenital abnormalities that cause portal-systemic shunts in children can be manifested by episodic hepatic encephalopathy, even without preexisting hepatic disease. Also, the cirrhotic patients with portal-systemic shunts develop encephalopathy easily compared with patients without portal-systemic shunts.

c. *Hepatic failure*

There have been many trials reporting that hepatic failure is the main cause of the development of hepatic encephalopathy, resulting from decreased hepatic functional capacity that diminishes the detoxification of ammonium, raising the plasma levels of this element, thereby producing the clinical manifestations of these patients.

d. Muscle

A reduction in the muscle mass of cirrhotic patients can predispose them to the development of hepatic encephalopathy. Muscle waste is explained not only by the presence of hepatic disease and the patient's nutritional status, but also by elevation of some cytokines like tumor necrosis factor-alpha (TNF-α), which in turn activates transcription factors like NK-a, resulting in reduced myosin synthesis. Muscle waste is associated with a lower metabolic capacity to detoxify ammonium and glutamine, resulting in the development of hepatic encephalopathy.

Brain alterations

a. *Osmotic*

Some studies have demonstrated that there are osmotic changes in patients with cerebral edema and hepatic insufficiency. On one hand the brain develops edema, raising intra cerebral pressure and producing herniation that can result in death. The glutamine produced because of the detoxification of ammonium in the astrocytes is considered an organic osmol that can cause edema in the astrocytes. It has been observed that the water channel aquaphorin-4 drives water into the cell. There is also evidence that the brain adapts to changes during chronic hepatic disease. Direct and indirect determinations of the organic osmoles using spectroscopy by resonance imaging in humans have demonstrated a loss of myo-inositol, taurine and glyceryl-phosphocholine, which are the

osmoles used by the astrocytes for the regulation the intracellular osmolality. These changes make the brain more vulnerable to a second osmotic change.

b. *Axonal communications*

There is also evidence of the important role of astrocytes in maintaining normal neuronal function. In hepatic encephalopathy there are no morphologic alteration in the neurons. The Alzheimer type II cells (astrocytes)can show some abnormalities: reduced activity of transporters (glutamate), increased expression of benzodiazepine receptors and increased monoamine oxidase (MAO) activity. As a result there are alterations in the metabolic communication between astrocytes and other cells. For example, astrocytes synthesize neurosteroids which activate GABA receptors and endogenous benzodiazepines receptors.

c. *Endothelial communication with astrocytes*: *brain blood flow and hepatic encephalopathy.*

Some experimental models have demonstrated an increase in cerebral perfusion in the presence of high levels of ammonium. This can be activated by intra-cerebral signals generated after the synthesis of glutamine in the astrocytes. Hypothermia and brain edema can also have an important role in the low cerebral perfusion demonstrated in experimental models. Cirrhotic patients have decreased brain blood flow,

probably secondary to peripheral vasodilatation. These alterations can cause a decrease in metabolic activity.

d. Other hypotheses

There are other hypotheses related to the pathogenesis of hepatic encephalopathy:

• *Ammonium*

Ammonium is fundamental to the pathogenesis of hepatic encephalopathy. After detoxification of ammonium by the astrocytes some neuro-chemical alterations occur. There are many factors that interact with ammonium, causing alterations in the astrocytes (hyponatremia, cytokine elevations, alterations in the ligands of astrocytes), thereby producing an anatomic substrate and neuro-chemical synergism that can increase the development of hepatic encephalopathy. However, ammonium levels do not correlate with the severity of encephalopathy.

•*Endogenous benzodiazepines*

The role of these substances in the alteration of GABA-ergic neurotransmission is not well understood. Some studies with flumazenil have not shown significant results; also, ammonium can activate GABA-ergic pathways by the synthesis of neurosteroids in astrocytes, as stated before.

• *False neurotransmitters*

A decrease in branched-chain amino acids can favor the entrance into the brain of aromatic aminoacids, which are precursors of false neurotransmitters that alter glutamine synthesis. The clinical experience with ramified amino acids is of great interest because it is possible that the amino acids have a direct effect in muscle, increasing ammonium detoxification. Other neurotransmission pathways involved in the development of hepatic encephalopathy are serotonin (5-HT), opiates and catecholamines. Other additional factors that can favor the development of recurrent hepatic encephalopathy episodes are nutritional status, especially in alcoholic patients who can have deficiencies in vitamins and micronutrients. One such example is a deficit in zinc, which is a cofactor in the urea cycle. Zinc supplementation, using a dose of 600 mg/day, has been studied in encephalopathy but has not demonstrated additional benefits[44]. However, it seems reasonable to measure the plasma zinc levels and add zinc supplementation when these are low. Another issue that has recently been studied is gastric colonization by *H. pylori*, a microorganism that produces urease. Eradication of *H. pylori* can be beneficial in other diseases, but it is not associated with a lower ammonium level or an improvement in hepatic encephalopathy.

To conclude, hepatic encephalopathy is the result of a combination of hepato-cellular insufficiency (live failure), toxin accumulation and the

establishment of a portal-systemic shunt. The main precipitating factor (without being an specific cause) is an altered level of plasma ammonium. The pathogenic mechanism includes the production of false neurotransmitters, facilitated sensibility of neurons by γ-aminobutyric acid (GABA),increases in the plasma endogenous benzodiazepines, diminished activity of urea cycle enzymes secondary to zinc deficiency and finally, manganese deposits on the basal ganglia.

Clinical stage

Generally, the diagnosis of hepatic encephalopathy is not difficult; the neurological exam is the main element to establish the diagnosis. As shown below although stage 2 shows symptoms such as lethargy, significant confusion and behavioral changes, in stage 1 the behavioral changes can be minimal, such as euphoria, confusion or some degree of depression. The more advanced stages can be manifested as confusion, somnolence and coma. Also, some electroencephalographic changes can be found that vary between the presence of triphasic waves and delta activity. Recently, an expert group on hepatic encephalopathy described a new classification for patients according to the type of hepatic alteration that causes the condition[35,36] with three different types of encephalopathy being considered:

Type A: Acute liver failure

Type B: Portal-systemic bypass without intrinsic

hepato-cellular disease (the more frequent)

Type C: cirrhosis and portal hypertension with porto-systemic shunts

Classification and grades of hepatic encephalopathy.

Grade I. Euphoria or depression, mild confusion, monotonous voice and/or sleep cycle disorders. Asterixis +

Grade II. Lethargy and/or confusion. Asterixis, triphasic waves on EEG

Grade III. Severe confusion, incoherent language, semi-stupor but awakes with language. Asterixis, triphasic waves on EEG

Grade IV. Coma, initially can respond to painful stimuli.Asterixis.Delta wave in EEG

Predisposing factors for development of hepatic encephalopathy.

Nitrogen products	Metabolic	Drugs	Other
GI bleeding	**Hypokalemia**	**Opiates**	**Infections**
Hiperazoemia	**Alkalosis**	**Diazepam**	**Surgery**
Constipation	**Hypoxia**	**Diuretics**	**Hepatopathies**
High protein diet	**Hyponatremia**	**Sedatives**	**Renal failure**
H. pylori	**Hyperkalemia**	**Phenol**	**Short-fatty acids**
Uremia	**Dehydration**		

In a patient with previously stable cirrhosis, hepatic encephalopathy is usually a consequence of an easily identified precipitating factor, as shown above, with gastrointestinal bleeding the more common etiologic factor. The frequency and form of presentation of encephalopathy in the same patient allows establishment of a predominant clinical course, within three possibilities:

1. Episodic: considered a “recurrent encephalopathy”

with precipitating factors or spontaneous delirium.

2. Persistent: cognitive deficits, extra-pyramidal manifestations,

sleep-pattern changes that cab be either mild

or severe, but always continuous.

3. Minimal: sub-clinical cases.

Hepatic encephalopathy is manifested in variable forms and can be associated with any neurological alteration, even with focal deficits. Frequently, there is cerebral edema that contributes to the clinical picture and increases the mortality in the patients with acute or chronic encephalopathy. The decrease in attention and changes of mental state can evolve to memory disorders, confusion, stupor and to coma; also, the varied combination of neurological signs include asterixis, rigidity, abnormal reflexes, Babinsky, and rarely, convulsions. One of the earliest signs of encephalopathy`is an inversion in the sleep cycle. Ammonium level is a key element in the diagnosis of hepatic encephalopathy, however its predictive value in cirrhotic patients is limited. Measuring the arterial levels and adjustment of the values according to the pH improve the predictive value, but these tests cannot be done in all hospitals. Recently, a relation between the levels of arterial ammonium and the development of brain herniation in acute hepatic failure has been demonstrated. Some other studies have shown that levels of more than

200 mg/dL of ammonium in hepatic encephalopathy stages III and IV are associated with cerebral herniation. However, other studies have shown no correlation between ammonium levels and the stage of hepatic encephalopathy. Generally, the diagnosis can be done by exclusion. There is no specific alteration in the hepatic function tests; the presence of high levels of ammonium in an adequate clinical context suggests the diagnosis. However, this is only true for hepatic encephalopathy stages III and IV (possibly II), in which the values are presented with the objective signs described before. This is not true for stages I or II, where objective signs cannot be perceived, allowing progression of the underlying condition. Also, it has been demonstrated that ammonium levels do not correlate with the severity of encephalopathy or with the response to treatment. For these reasons, imaging studies are suggested to diagnose encephalopathy stage I and stage II (or mild and minimal-persistent). Brain resonance imaging can demonstrate manganese deposits at the basal ganglia, showing a high resonant globus pallidus. Computed tomography is used to examine the presence of atrophy or cerebral edema. Positron emission tomography can produce images reflecting biochemical or physiological processes. Finally, spectroscopy by resonance imaging makes evident the elevations in the spike of glutamine/glutamate and diminished myo-inositol and choline. This data can help treatment halt the progression of encephalopathy. Certain

neuropsychological tests have been approved by the majority of investigators but still require formal validation:

1. Numeric connection A and B

2. Line drawing

3. Digital symbols and points following.

These types of tests have been named the PHES (Psychometric hepatic encephalopathy score) and can be done in ten minutes. The main objective is to evaluate the reaction time and the accusiocity, visual construction, concentration, attention and memory.

Treatment

The treatment of patients with chronic hepatic encephalopathy includes establishing the therapeutic objectives. In recurrent encephalopathy the main objective is to avoid the acute episodes, while in the persistent form the objectives are toward improvement of chronic symptoms and quality of life. There are objective parameters that allow good characterization of the effects of treatment. One such parameter is the number of days that the patient's autonomy is limited compared to his or her basal state (for example, whether he or she is able to work, walk, eat or clean him or herself without help). According to the optimal level for an individual patient, the degree of autonomy loss can be estimated (as an example: 25% not able to work, 50% not able to walk, 75% needs help to eat). There are tables developed to evaluate patients with dementia that can be

useful in these circumstances (**Barthel** scale). In the best case, some psychometric tests and neuropsychological testing should also be done, so as to evaluate the effects of the chronic manifestations. The treatment of hepatic encephalopathy should be accompanied by the treatment of the other complications of cirrhosis. The potential effects of the treatment should be considered against the risk of developing hepatic encephalopathy. In patients with ascites, it is better to perform paracentesis or to use diuretics. When prescribing diuretics, they should be used in low doses that can be modified according to the response. It is useful to keep a record of the weight of the patient, the diuretic dose and the neurological manifestations. The patient and his or her family should understand that it is better to have mild edema than frequent development of encephalopathy. Between the different choices in the treatment of patients with gastrointestinal hemorrhage, endoscopic or pharmacological treatments are better options than the ones that increases the portal-systemic shunts (surgery or TIPS), because between 30 and 40% of the patients with TIPS can develop hepatic encephalopathy. The development of hepatic encephalopathy is considered a sign of a bad prognosis. For this reason, patients who have presented with an episode of hepatic encephalopathy should be evaluated as candidates for hepatic transplantation[6]. However, in cases of chronic persistent encephalopathy, the decision can be difficult. Dementia and other severe neurological

signs such as paraplegia or psychiatric manifestations are considered irreversible. There are descriptions of some cases that show improvement of lesions after the transplant. The decision should be individualized for each patient. One group of patients with chronic encephalopathy is characterized by the development of hepatic encephalopathy after the surgery for a portal-systemic shunt. Part of the treatment objectives for patients with hepatic encephalopathy is the importance of applying some general measures to support the patient. nursing care, in selected cases the use of prophylactic endotracheal intubation, and during the period of altered mental state, proper nutritional support. Also, it is important to identify and treat the potential precipitating factors. In the context of gastrointestinal hemorrhage, searching for occult fecal blood or clinical evidence of hemorrhage, the detection of infections specifically of ascites; additionally, correction of renal and electrolytes disturbances, avoiding the use of psychoactive medications such as benzodiazepines, narcotics and sedatives and preventing constipation with the use of laxatives. Besides these measures, the patient should follow some dietary recommendations and receive non-absorbable disaccharide. In some cases, the use of neomycin, other antibiotics or dopaminergic drugs can be useful. However, none of these therapeutic measures has been evaluated with clinical trials of appropriate design and a significant number of patients. Accordingly, all of these measures have been

criticized. However, clinical experience, together with the data presented in the scientific literature allows some recommendations about their use.

Treatment options

• Diet 1.2 grams of protein/kg/day (1-1.5 grams)

Non-absorbable disaccharide

• ***Lactulose***

• Acute Oral: 45 mL each hour until bowel movement and clinical improvement

• Chronic Oral: 15-45 mL tid or bid continuous until 2 to 3 bowel movements per day

• **Lactose**

• Acute 20% enemas 200 g/L liter of isotonic solution until clinical improvement

• Chronic Oral: 30 g tid or bid continuous until 2 to 3 bowel movements per day

• **Sodium benzoate** Oral: 5 g bid until clinical improvement

• **orinithine-aspartate** Oral or IV 9 gr/d until clinical improvement

Antibiotics

• **Neomycin**

• Acute Oral: 3.6 g/day 1-2 weeks

• Chronic * Oral: 1-2 g/day

• **Metronidazole** ** Oral: 250 mg/day

• **Flumazenil** I.V.: 1 mg

• **Bromocriptine** Oral: 30 mg bid Continuous in case of no response with other treatments

MATERIALS AND METHODS:

STUDY DESIGN:

Prospective, descriptive study

PLACE & DURATION:

Department of Medicine and Gastroenterology, Government Stanley Hospital Chennai

STUDY PERIOD:

Study was done over a period of one year from june 2007 to june 2008

PATIENT & PROCEDURE:

INCLUSION CRITERIA:

1.Patients with cirrhosis of liver, belonging to either sex

2.age above 12 years

3.hepatic encephalopathy including minimal hepatic encephalopathy

EXCLUSION CRITERIA:

1. Patients with psychiatric disorders or on treatment for psychiatric disorders

2.Those with altered sensorium due to metabolic disease or head injury

3.Acute alcoholic intoxication and alcoholic withdrawal states

PROCEDURE

For data collection, a questionnaire was developed. A detailed clinical history of the patient was taken regarding the present and past illnesses . Questions were asked about gastrointestinal bleeding, including haemetemesis and melaena, constipation, vomiting, dirrhoea, oliguria, fever, bleeding manifestation, high protein diet, paracentesis and any trauma or surgery. Personal history about alcohol consumption was noted in along with smoking and i.v drug abuse Use of any sedatives, diuretics, tranquilizers, analgesics and cough syrups was also inquired in detail. All patients were carefully examined with special attention to jaundice, anaemia, fever, asterixes, hydration, pedal odema, and ascites. Detailed abdomen system and neurological examination was done on all patients. Encephalopathy was graded according to the clinical criteria as given in Table A.

Table A: Clinical Grades of hepatic encephalopathy

Grades	Description
I	Mild confusion, euphoria, anxiety or depression, reversed sleep rhythm, slurred speech
II	Drowsiness, lethargy, gross deficits in ability to perform mental tasks, relatively moderate confusion
III	Somnolent but rousable, severe confusion, inability to perform mental tasks.
IV	Coma with (IVa) or without (IVb) response to painful stimuli

For each patient full blood count, liver function tests, renal function tests, random blood sugar, serum electrolytes, serum albumin and coagulation

profile were carried out. An abdominal ultrasound was done to look for liver and splenic size, parenchymal echogenicity, portal vein diameter, and ascites. In case of ascites, an ascites tap was also done to look for spontaneous bacterial peritonitis. Any evidence of the presence of other co-existent complications of cirrhosis liver was also recorded and Child's score was assessed for each patient based on parameters in table B

Table B: Child Pugh scoring criteria

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 numerical score Child Pugh Class

5-6 -- A

7-9 -- B

10-15 -- C

All patients were followed for the duration of their stay in hospital and whether they survived or died at the end of the stay was also recorded.

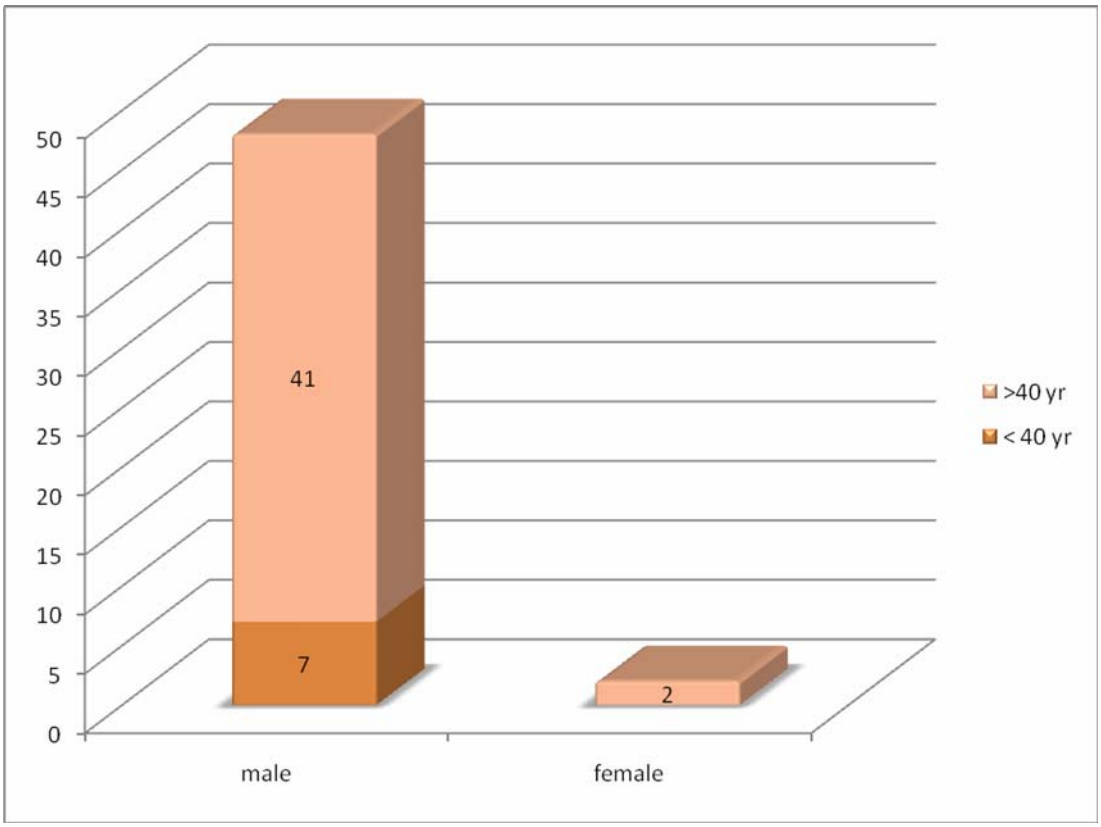
OBSERVATION & DATA ANALYSIS

A total of 50 admitted patients, including 48(96%), male and 02(4%) females, presenting or complicating into hepatic encephalopathy were studied. Majority i.e. 43(86%) patients were older than 40 years including 41 (82%) males and 02(04%) females in this group. Seven (14%) patients were between 20 and 40 years old, all of them were males. The age and gender distribution in different clinical presentation grades of patients with HE is given in Table 1.

Table – 1

Age	Male	Female
< 40 years	07	0
> 40 years	41	02

Table 1: Age and Gender distribution



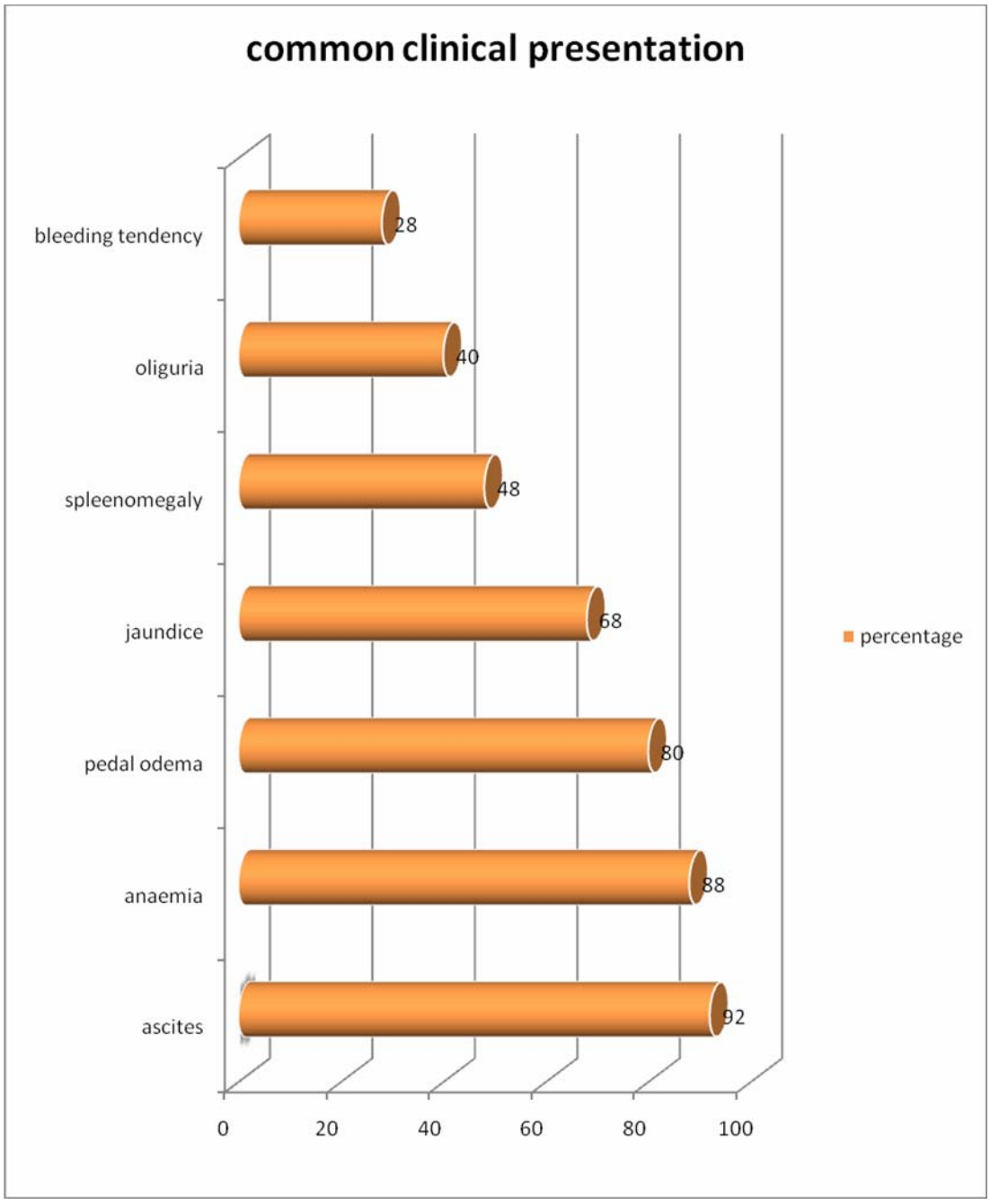
Age and Gender distribution

Most common presenting clinical features in the patients were ascites. Other common presentation is given in table 2

Table 2

Clinical features	Frequency
Ascites	46 (92%)
Anemia	44 (88%)
Pedal odema	40 (80%)
Jaundice	34 (68%)
Spleenomegaly	24 (48%)
Oliguria	20 (40%)
Bleeding tendency	14 (28%)

Table 2: common presenting features in patients


common clinical presentation
bleeding tendency
oliguria
spleenomegaly
jaundice
pedal odema
anaemia
ascites
28
40
48
68
80
88
92
0
20
40
60
80
100
percentage

When cirrhotic patients were grouped into Child Pugh classification[6],64% of the patients were found to be in Class C, 28% of patients in Class B, 8% of patient in class A,as shown in Table 3

Table – 3

Child pugh class	No of patients	Percentage(%)	No of patients acc to age group			
			< 40 years		< 40 years	
			M	F	M	F
Class A	04	08%	0	0	2	2
Class B	14	28%	4	0	10	0
Class C	32	64%	3	0	29	0

Table 3: Frequency according to child's classification and associated age and gender distribution

Table - 4

Child pugh class	No of patients	Percentage(%)	No of patients acc to age group			
			< 40 years		< 40 years	
			M	F	M	F
Grade 1	04	08%	0	0	2	2
Grade 2	18	36%	2	0	16	0
Grade 3	16	32%	1	0	15	0
Grade 4	12	24%	4	0	08	0

Table 4: Age and gender distribution in different clinical presentation grades of patient with hepatic encephalopathy

The precipitating factors of hepatic encephalopathy most commonly found in this patients were GI bleeding 30 (60%), electrolyte disturbance 20 (40%), infection 10 (20%) and constipation 8 (16%).Out of a total of fifty patients of HE, no factors could be found in 2 (4%) patients, 18 (36%) patients had one factor; 16 (30%) had two factors, while 12 (24%)patients had more than two precipitating factors. 46 (92%) patients have associated ascites, 4(8%) had spontaneous bacterial peritonitis, 6 (12%)patients had hepatorenal syndrome, while in 1 (2%) patient hepatopulmonary syndrome was diagnosed. In the analysis of the laboratory findings, hyponatremia, hypokalemia, hypoglycaemia and low

haemoglobin were found in 16 (32%), 10 (20%), 4 (8%), and 44 (88%) patients respectively. In 35(70%) patients blood urea was found high while creatinine was above normal limits in 31 (62%) patients. Hypoalbuminemia (serum albumin <3.3 g/dl) was found in 43 (86%) patients. Leukocytosis (total leukocyte count >11000/ μL) was a feature in the laboratory data of 20 (40%) patients. The rest of the patients had either normal or low TLC count. Coagulation profile was abnormal in a fraction of patient with 14 (28%) patients having Prothrombin time >5 seconds. However thrombocytopenia (platelet count <150,000/ μL) was a consistent finding in 36 (72%) patients.

Table - 5

Precipitating factor	No of patients (%)
Gastrointestinal bleed	30 (60%)
Hyponatremia	16 (32%)
Hypovolemia	10 (20%)
Infection	10 (20%)
Hypokalemia	10 (20%)
Constipation	08 (16%)
Diarrhoea	04 (08%)
Metabolic acidosis	04 (08%)
Diuretics	04 (08%)
Sedatives	02 (04%)
Hypoglycemia	02 (04%)
No factors	02 (04%)

Table 5: precipitating factors for hepatic encephalopathy

HBsAg was found solely positive in 4 (8%), HCV antibodies were found positive alone in 8 (16%) patients, 2 (4%) patients had both B and C positive, while 38 (76%) had neither B nor C. 38 patients were chronic alcoholic taking more than 80 mg of alcohol per day for more than twenty years.

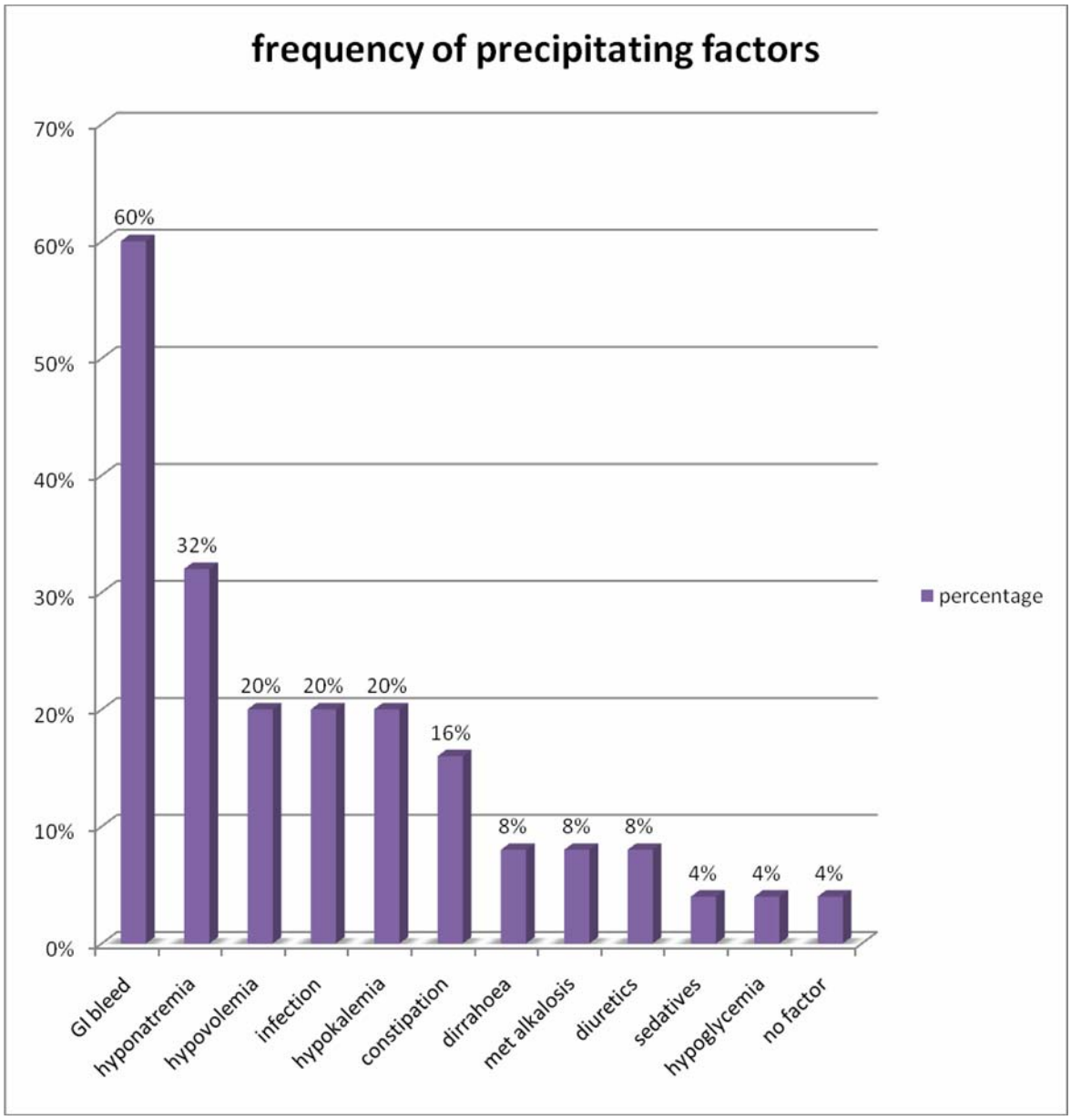

frequency of precipitating factors
70%
60%
50%
40%
30%
20%
10%
0%
60%
32%
20%
20%
20%
16%
8%
8%
8%
4%
4%
4%
GI bleed
hyponatremia
hypovolemia
infection
hypokalemia
constipation
dirrahoea
met alkalosis
diuretics
sedatives
hypoglycemia
no factor
percentage

Table – 6

Etiology of cirrhosis	No of patient (%)
Alcohol Intake	38 (76%)
Hepatitis C	08 (16%)
Hepatitis B	04 (08%)

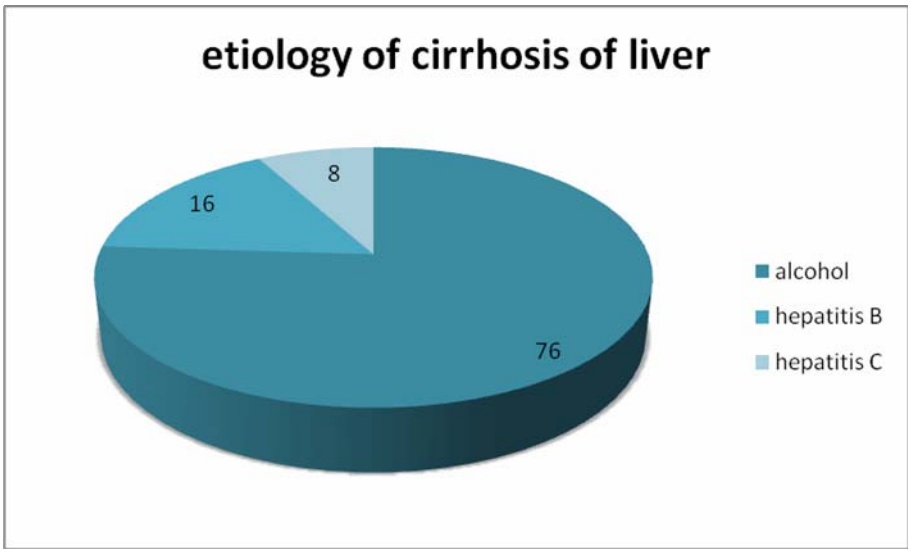
Table 6: various etiology factor in cirrhosis of liver

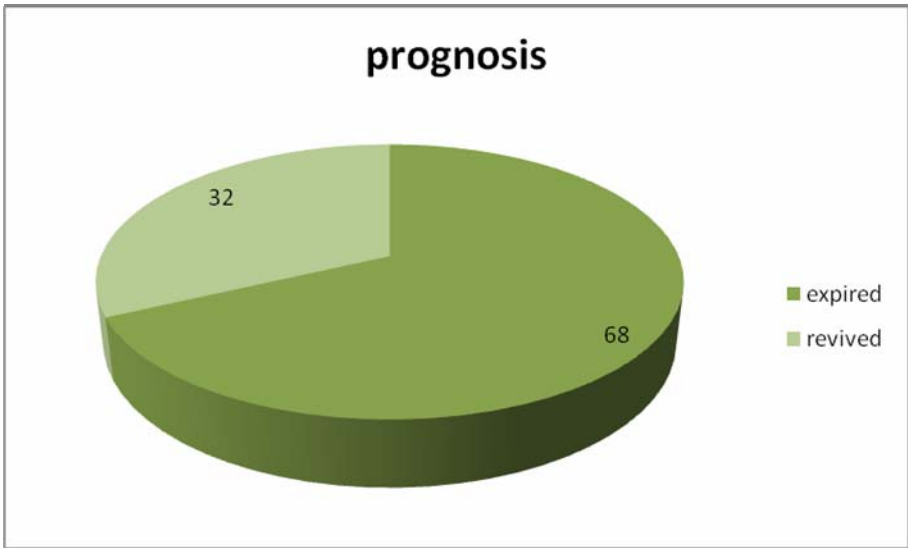
Out of all the 50 patients 34 (48%) died, all of them males. 12 patients were in HE grade 3 and 10 patients were in grade 4. All cirrhotic patients who expired were found to be in Class C of Child's

Table - 7

Patient prognosis	No of patient (%)
Expired	34 (68%)
Revived	16 (32%)

Table 7: prognosis of patient with hepatic encephalopathy in this study


etiology of cirrhosis of liver
8
16
76
alcohol
hepatitis B
hepatitis C


prognosis
32
68
expired
revived

DISCUSSION

Hepatic Encephalopathy has never been less than an unsolved mystery for physicians and researchers around the globe. Since the time of Hippocrates it has been difficult to diagnose and manage any patient of hepatic encephalopathy. Although the exact pathogenic mechanism is yet to be determined, modern research has proved time and again that identifying and removing precipitating factors is still the key step in the overall management[11].

In our study that was conducted on 50 patients, majority (86%) of patients were more than forty years old. **Durrani**[12] had a similar finding in the province of Balochistan,pakistan.

Male dominance in progression to advanced stages of chronic liver disease was found in our patients. **Al-Gindan**[13] also reported the same pattern in a study in Saudi Arabia.

The most common cause of Cirrhosis liver in this study is Alcohol intake. 38(76%) person were alcoholic, compared to 12(24%) non alcoholic.This is in conjuction with the studies done in industrialized nations of the west, **conn**[18] and **faloon**[19] ,which showed alcohol as the main aetiological factor[15].

Hepatitis B was an uncommon cause of cirrhosis in our study but Hepatitis C twice more common than Hepatitis B as a cause of cirrhosis of liver in this study. A probable explanation could also be that most of our patients were at end stage cirrhosis in which hepatitis C is the commonest cause, This is especially true for the province of Punjab where **Aisha**[23] and **Khurram**[25] reveal gastrointestinal bleeding, infection and constipation as the main factors.

Studies done by **Shaikh**[22] and **Hameed**[24] show electrolyte imbalance ranked at the top. Infection, gastrointestinal bleeding and have been repeatedly demonstrated as important precipitating factors of HE[16,17] a fact also borne out by our study. The findings of the frequencies of different precipitating factors in different national and international studies are given in Table 8.

Table 8

Studies	GI bleed (%)	Infection (%)	Hyponatremia (%)	Hypokalemia (%)	Constipation(%)	Diarrhea (%)
Fallon[19]	33	-	-	18	6	-
Conn[18]	18	04	-	09	3	12
Shaik[22]	56	15	20	70	52	22
Hameed[24]	56	28	28	68	52	-
Souheil[20]	18	03	-	11	03	-
Aisha[23]	76	52	-	-	36	-
Alam[14]	22	24	24	18	32	-
Khurram[9]	31	11	33		33	-
Present study	60	20	32	20	16	08

It can be assessed from the table that our findings match those studies done in this sub-continent, Out of four foreign studies however reveal infection as a less common cause abroad, which is understandably due to better hygienic conditions of the patients and hospitals in the western countries.

In 4 % patients, no precipitating factors could be found. In such patients exploration should include Doppler Ultrasonography to search for large spontaneous portosystemic shunts which can be confirmed and treated

with angiographic techniques[26]. Occult precipitating factors such as zinc deficiency should also be sought.[27]

32% of our patients had hyponatremia and 20% were hypokalemic. This was due to the fact that most of them were on diuretics and there was associated diarrhoea or vomiting contributing to the electrolyte disturbances.

Findings of low haemoglobin, thrombocytopenia and hypoalbuminemia correspond well with advanced stages of cirrhosis.[28] Raised total leukocyte count in 40% of patients, supports infection[23] as a common precipitant in our settings.

Raised urea and creatinine is seen in 28% of patients, highlight the fact that azotemia is an important pathogenic contributor to the onset of HE[29].

The mortality rate in our patients was 68%, which is double than what repoted by **Sheila Sherlock[6]**. who did expire were mostly in Class C of Child's classification and grade 3 or 4 of hepatic coma.

Gastrointestinal bleeding, electrolyte disturbances, infection, constipation are the most common factors of hepatic encephalopathy in this study.

Priority should be given to these factors in terms of hospital funds, medicines and human efforts.

Caution must be exercised in putting cirrhotic patients on diuretics.

Early and effective infection control measures and better hygienic conditions in government hospitals are needed to be maintained.

Consistent use of lactulose and fibre should be encouraged to prevent constipation.

More and more endoscopic facilities should be made available nationwide for prompt control of gastrointestinal bleeding.

Most importantly, a more committed effort is the need of the hour to control increasing incidence of hepatitis C.

Only then we stand any chance of combating cirrhosis and even worse hepatic encephalopathy.

CONCLUSION

1. In this study 96% of patient were males and 4% of patient were females.
2. 86% of the patients were more than 40 years of age.
3. Most common etiological factor for cirrhosis of liver was alcohol intake.(76%)
4. Most common clinical presentations were ascites(92%) and anaemia(88%).
5. Most common precipitating factor was GI bleed(60%).
6. Other important precipitating factor hyponatremia(32%), infection(20%), hypovolemia(20%), hypokalemia(20%), constipation(16%).
7. Less common precipitating factors were dirrhoea(8%), diuretics(8%), acidosis(8%), sedatives(4%), hypoglycemia(4%).
8. 36% patients had one precipitating factors for hepatic encephalography.
9. 30% patients had two precipitating factors for hepatic encephalography.
10. 18% patients had more than two precipitating factors for hepatic encephalography.

11. 4% of patient no precipitating factors was found for hepatic encephalopathy.

12. Azotemia was also a important precipitating factor seen in 28% of patient.

13. 64% of patient were classified in class C of child-pugh classification.

14. 36% of patients were in grade 2 and 32% of patient were in grade 3 of hepatic encephalopathy grading.

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PROFORMA

Name:

Occupation:

Age:

Literacy status:

Sex:

Per capita income:

DOA:

DOD:

Outcome: Recovered/expired/not known

Clinical Diagnosis:

History:

Fever

Altered sleep rhythm

Malaise

Anorexia

Nausea

Vomiting

Abdominal pain

Diarrhea

Skin rashes

Pale stools

Distaste for smoking

Constipation

Large protein intake

Itching

Cough with sputum

Burning micturition

Precipitating factors of hepatic encephalopathy

GI bleed: haemetemesis/malena/

Constipation:

Diarrhea:

Overdiuresis

Large paracentesis

High protein diet

Surgery

Hypovolemia

Hypoxia

Hyponatremia

Hypokalemia

Metabolic alkalosis

Infections:chest/UTI/SBP

Drugs:sedative/NSAIDS/cough syrup

Superimposed acute liver disease

Past History:

DM/HT/CAD/PT

Similar illness

Contact with cases of viral hepatitis

Recent surgery

Treatment History:

IV fluids/injections/admission to hospital

Large paracentesis:

Diuretics

Native treatment

Family History:

Jaundice

Liver diseases

Cancers

Personal History:

Diet:

Smoking:

Ethanol:

IV

drug

abuse

Drug intake: sedatives

Examination:

Consciousness: conscious/semiconscious/unconscious

Orientation: person/place/time

Anaemia:

Hydration:

Cyanosis: central/peripheral

Clubbing:

Lymphadenopathy:

Tattoo marks

Signs of liver disease:

Jaundice

Coagulopathy

Edema legs

Spider angioma

Fetor hepaticus

Palmar erythema

Asterixis:

Vital signs:

Temperature:

Pulse:

BP:

RR:

Abdomen:

Oral cavity:

Parotid gland:

Dilated veins:

Liver:

Spleen:

Ascites:

Other systems:

CNS

Higher function: Appearance/behaviorur/attention

Delusion/hallucination

Euphoria/ depression

Orientation:person/place/tim

Memory:

Intelligen

Speech:

Hepatic encephalopathy stage:1/2/3/4/

Cranial Nerves

Motor system:

Nutrition

Tone

Power

Superficial reflex:

Deep tendon reflex:

Sensory system:

Involuntary movement

Meningeal sign:

Skull & spine:

CVS: S1S2,

RS:

INVESTIGATION

1)Haemogram

HB: TC: DC:

ESR : PCV: PLATELET:

2) Urine: Alb: Sugar: Deposits: BS:

BP:

3) LFT: T.Bil: D.Bil: SGOT: SGPT:

ALP: S.Alb: S.Glb: GGT:

4) Coagulation profile: BT: CT: APTT:

PT:

5) RFT: B.Sugar: Urea: Creat: Na: K: Cl: HCO3:

6) Ascitic fluid analysis: Glucose: Cell count: Culture:

SAAG: Stain:

7) X-ray chest : ECG:

8) USG Abdomen:

9) Urine culture:

10) Blood culture:

11) Sputum culture:

12) EEG:

13) CT Abdomen:

14) MRI:

15) Other investigation:

TREATMENT GIVEN :

ABBREVIATIONS

HE – hepatic encephalopathy

CLD- chronic liver disease

HbSAg- hepatitis B antibody

HCV- hepatitis C virus

FHF- fulminant hepatic failure

TIPS- trans jugular intrahepatic porto-systemic shunt

TGF- tumour growth factor

PBC- primary biliary cirrhosis

UGI- upper intestinal bleed

AST- aspartate transaminase

ALT- alanine transaminase

PHT- portal hypertension

TNF- tumour necrosis factor

NK- natural killer cells

H.pylori- helicobacter pylori

HBV- hepatitis B virus

EEG- electroencephalography

Master chart- 1- present

2- absent