PRECIPITATING FACTORS FOR HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER-A ONE YEAR CROSS SECTIONAL STUDY

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ENDORSEMENT

This is to certify that the dissertation entitled **PRECIPITATING FACTORS FOR HEPATIC ENCEPHALOPATHY IN CIRRHOSIS OF LIVER-A ONE YEAR CROSS SECTIONAL STUDY** is a bonafide research work done by **REG NO. BG0114003**

Dr. REKHA S PATIL MD
Professor and Head,
Department of Medicine,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi.

Dr. N. S. Mahantshetti MD
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi.

HE	:	Hepatic Encephalopathy
HRS	:	Hepatorenal syndrome
CL	:	Cirrhosis of Liver
WHC	:	West Haven Criteria
ALF	:	Acute Liver Failure
ACLF	:	Acute on Chronic Liver Failure
NH3	:	Ammonia(unionised)
NH4+	:	Ammonium ion
GLU	:	Glutamate
GLN	:	Glutamine
GNASE	:	Glutaminase
BBB	:	Blood-brain barrier
GABA	:	Gamma-amino-butyric acid
Ach	:	Acetylcholine
Ach E	:	Acetylcholine esterase
OHE	:	Overt Hepatic Encephelopathy
GCS	:	Glasgow Coma Scale
CHE	:	Covert Hepatic Encephelopathy

MHE : Minimal Hepatic Encephelopathy

PSE : Portosystemic Encephelopathy

PHES : Psychometric Hepatic Encephalopathy Score

CFF : Critical Flicker Frequency

CRT : Continuous Reaction Time

ICT : Inhibitory Control Test

BCAAs : branched-chain amino acids

LOLA : L-ornithine Laspartate

GPB : Glyceryl phenylbutyrate

ABSTRACT

Purpose: Hepatic encephalopathy(HE) describes a spectrum of potentially reversible neuropsychiatric abnormalities in patients of cirrhosis of liver. HE is a well recognised clinical complication of cirrhosis of liver and the prompt identification of well defined precipitating factors is extremely important in diagnosis and treatment of this fatal condition

Objectives: To study precipitating factors for hepatic encephalopathy in cirrhosis of liver.

Methodology: A cross sectional study was conducted in patients presenting to Department of Internal medicine at KLES Dr Prabhakar Kore Hospital & MRC, Belgaum fulfilling inclusion criteria, for hepatic encephalopathy with cirrhosis of liver and subjected to detailed history, examination and processed through necessary investigations with informed consent

Results: In this study infection (SBP + other infections) 41.66%(35) is the commonest precipitating factor for HE, followed by electrolyte imbalance34.52(29), upper GI bleeding with 32.14%(27) of patients and constipation 4.76%(4). Among the infections spontaneous bacterial peritonitis 21.43%(18) is the commonest precipitating factor followed by other infections 20.41%(17) like cellulitis of extremities and abdominal wall 9.52%(8) , 5.95%(5) cases are pneumonia, 2 are of acute gastroenteritis and other 2 are undiagnosed but presented with fever and raised leucocyte count.

In electrolyte imbalance hyponatremia16.67%(14) is the most commonest electrolyte disturbance causing HE. In our study hypomagnesaemia 8.33%(7 cases) is seen as precipitating factor for HE.

Among the participants (N=84) Grade I HE is seen in only 2 cases, 58.33%(49 patients have grade II hepatic encephelopathy, 34.52%(29) have grade III HE, 4.76%(4) have grade IV HE.

Grade I HE showing equal association with single and multiple precipitating factors, Grade II HE,43 (83.67%) were having single precipitating factor. 65.5% of patients of Grade III HE had single precipitating factor. All Grade IV, were assosciated with single precipitating factor. There is no correlation of Grade of HE to number of precipitating factors.

Among 2 patients of Grade I, one was having infection. Among 49 patients of Grade II 23(46.94%) were having infection. Among 29 patients of Grade III 10(34.48%) were having infection. Among 4 patients of Grade IV only 1 patient was having infection. In 84 patients of HE,35(41.67%) were precipitated by infection,. in which Grade II was common.

In our study 27 patients had upper GI bleed. 19 patients (out of 27) had Grade III HE. 29 patients had electrolyte imbalance. 21 patients (out of 29) had Grtade II HE.

In our study 57.14%(48) patients had Child Pugh class B and 42.86%(36) had Child Pugh class C. As grade of HE increases so does child Pugh score and child Pugh class is directly proportional to grade of HE.

Conclusion: Infection is the commonest risk factor for hepatic encephalopathy, followed by electrolyte imbalance, upper GI bleeding, HRS, and constipation.

Grade II HE is the most common presentation seen in this study.There is no correlation of Grade of HE to number of precipitating factors. There is no correlation of Grade of HE to infection. Upper GI bleeding patients had presented mostly with Grade III HE. Electrolyte imbalance had presented mostly with Grade II HE.

In our study we observed that hypomagnesemia is a precipitating factor for HE. Role of magnesium in causing HE in patients of CL is important as correction of it shows a dramatic response. So monitoring of serum magnesium level is important in a patient with HE. As sample size of present study is small larger studies are required to confirm the role of magnesium as a precipitating factor for HE in cirrhosis of liver patients.

Limitations:

- Sample size was small to generalize the study result.
- This study was done in a short period, so all factors in relation to precipitating factors for HE in CL cannot be studied.
- Study was conducted only in single centre . So this study result would not be generalized for the entire country.

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INTRODUCTION

Hepatic encephelopathy(HE) is a syndrome observed in patients with cirrhosis of liver. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of brain disease[1].Hepatic encephalopathy (HE) is present in upto 70% of all patients with cirrhosis, including patients with abnormalities demonstrable only by psychometric testing[2]. It accompanies portal-systemic shunting of venous blood that occurs either spontaneously, due to portal hypertension, or surgically following porto-caval anastomosis surgery or trans-jugular intra-hepatic porto-systemic stent shunt (TIPS) aimed at relieving portal hypertension. About 30% of patients with cirrhosis of liver die due to hepatic coma. A precipitating factor can be usually identified for acute HE in cirrhosis of liver patient and the treatment of the episode is directed towards the correction of this precipitant. Once the precipitating condition has been resolved, the encephalopathy also subsides usually.[3] Hepatic Encephalopathy could be acute, sub acute, or chronic or it may be clinical or subclinical.

Historically, the role of ammonia accumulation has dominated explanations of the pathogenesis of HE. However over the past decade evidence has emerged for a role of other concurrent factors (such as inflammation, hyponatraemia) in the development of HE. HE is a well

recognized clinical complication of cirrhosis of liver and the presence and prompt identification of well defined precipitating factors is extremely important in diagnosis and treatment of this fatal condition. About 30% of patients with cirrhosis of liver die due to hepatic coma.[4]

Five years after the diagnosis of cirrhosis, there is 26% probability for developing at least one episode of HE[5]. HE is also a common problem after insertion of a transjugular intrahepatic portosystemic shunt (TIPS)[6,7]. Despite the impressive advances in our understanding of the several pathophysiological mechanisms which are involved in HE, the treatment options remain an unmet clinical need, accompanied by considerably high mortality rates. After the first clinical manifestation of HE, the patients' prognosis is very poor; probability of five-year survival is 16% to 22%, compared with that of 55% to 70% in cirrhotic patients without HE[5,8].The pathophysiology of chronic HE is apparently multifactorial, with several circulating neurotoxins being involved. The systemic accumulation of ammonia neurotoxic concentrations seems to be the most prominent factor[9,10], while the inter organ ammonia and amino acid metabolism is of pivotal importance in the pathogenesis of HE. Since Nencki and Pavlov described meat intoxification in portacaval shunted dogs over 100 years ago[11]ammonia has been considered as a central factor to the pathogenesis of HE[12] The

clinical importance of hyperammonemia's role in patients with liver failure is no more evident than in the observation that ammonia levels of >150 μmol/L predict brain herniation, coma and death in patients with ALF[13]. Several treatment agents such as lactitol, lactulose, L-ornithine-L-asparate and rifaximin aim to lower blood and cerebral ammonia levels and thereby attenuate its toxic effects.

1.2 Research Question

What are the precipitating factors for hepatic encephalopathy in alcoholic cirrhosis of liver?

Frequency of precipitating factors in hepatic encephalopathy in ethanol related cirrhosis of liver?

1.3 Objectives

1.3.1 General objective

To explore the common precipitating factors for hepatic encephalopathy in cirrhosis of liver

1.3.2 Specific objectives

To determine the weather calcium and magnesium can cause HE in cirrhosis of liver, and frequency of other precipitating factors.

1.4 Operational definition

HEPATIC ENCEPHELOPATHY

HE refers to a complex and potentially reversible or progressive syndrome of cerebral dysfunction, which consists of neuropsychiatric, cognitive and motor components, characterized by a broad etiological spectrum. It is observed in cirrhotic patients and those with acute liver failure (ALF) in the absence of other known brain disease, as a result of decompensated liver function.[1]

OBJECTIVES

1. To study precipitating factors for hepatic encephalopathy in cirrhosis of liver.

REVIEW OF LITERATURE

Hepatic encephalopathy (HE) is a frequent complication and one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers. Furthermore, cognitive impairment associated with cirrhosis results in utilization of more health care resources in adults than other manifestations of liver disease.[14] Progress in the area has been hindered by the complex pathogenesis that is not yet fully elucidated. Apart from such biological factors, there remains the larger obstacle that there are no universally accepted standards for the definition, diagnosis, classification, or treatment of HE, mostly as a result of insufficient clinical studies and standardized definitions.

DEFINITION OF THE DISEASE/CONDITION

OVERVIEW

Advanced liver disease and portosystemic shunting (PSS), far from being an isolated disorder of the liver, have well-known consequences on the body and, notably, on brain functioning. The alterations of brain functioning, which can produce behavioral, cognitive, and motor effects, were termed portosystemic encephalopathy (PSE)[15] and later included in the term HE.[16] Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence.[17,18] Even in its mildest form, HE reduces health-related quality of life and is a risk factor for bouts of severe HE.[19-21]

DEFINITION OF HE

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma. This definition, in line with previous versions,[22,23] is based on the concept that encephalopathies are “diffuse

disturbances of brain function"[17] and that the adjective "hepatic" implies a causal connection to liver insufficiency and/or perihepatic vascular shunting.[18]

EPIDEMIOLOGY

The incidence and prevalence of HE are related to the severity of the underlying liver insufficiency and PSS.[24-27] In patients with cirrhosis, fully symptomatic overt HE (OHE) is an event that defines the decompensated phase of the disease, such as VB or ascites.[19] Overt hepatic encephalopathy is also reported in subjects without cirrhosis with extensive PSS.[20,21] The manifestation of HE may not be an obvious clinical finding and there are multiple tools used for its detection, which influences the variation in the reported incidence and prevalence rates. The prevalence of OHE at the time of diagnosis of cirrhosis is 10%-14% in general,[28-30] 16%-21% in those with decompensated cirrhosis,[19, 31] and 10%-50% in patients with transjugular intrahepatic portosystemic shunt (TIPS).[32,33] The cumulated numbers indicate that OHE will occur in 30%-40% of those with cirrhosis at some time during their clinical course and in the survivors in most cases repeatedly.[34] Minimal HE (MHE) or covert HE (CHE) occurs in 20%-80% of patients with cirrhosis.[35-39].The prevalence of HE in prehepatic noncirrhotic portal hypertension (PH) is not well defined. The risk for the first bout of OHE is 5%-25% within 5 years after cirrhosis diagnosis, depending on the presence of risk factors, such as other complications to cirrhosis (MHE or CHE, infections, VB, or ascites) and probably diabetes and hepatitis C. Subjects with a previous bout of OHE were found to have a 40% cumulative risk of recurring OHE at 1 year,[40] and subjects with recurrent OHE have a 40% cumulative risk of another recurrence within 6 months, despite lactulose treatment. Even individuals with cirrhosis and only mild cognitive dysfunction or mild electroencephalography (EEG) slowing develop approximately one bout of OHE

per 3 years of survival.[41,42] After TIPS, the median cumulative 1-year incidence of OHE is 10%-50%[43,44] and is greatly influenced by the patient selection criteria adopted.[45] Comparable data were obtained by PSS surgery. It gives an idea of the frequent confrontation of the health care system by patients with HE that they accounted for approximately 110,000 hospitalizations yearly (2005-2009)[46] in the United States. Though numbers in the European Union (EU) are not readily available, these predictions are expected to be similar. Furthermore, the burden of CLD and cirrhosis is rapidly increasing,[47,48] and more cases will likely be encountered to further define the epidemiology of HE.

CLINICAL PRESENTATION

Hepatic encephalopathy produces a wide spectrum of nonspecific neurological and psychiatric manifestations.[22] In its lowest expression, HE alters only psychometric tests oriented toward attention, working memory (WM), psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures.[49] As HE progresses, personality changes, such as apathy, irritability, and disinhibition, may be reported by the patient's relatives, and obvious alterations in consciousness and motor function occur. Disturbances of the sleepwake cycle with excessive daytime sleepiness are frequent,[50] whereas complete reversal of the sleep-wake cycle is less consistently observed. Patients may develop progressive disorientation to time and space, inappropriate behavior, and acute confusional state with agitation or somnolence, stupor, and, finally, coma.[51] The recent ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus uses the onset of disorientation or asterixis as the onset of OHE. In non comatose patients with HE, motor system abnormalities, such as hypertonia, hyper-

reflexia, and a positive Babinski sign, can be observed. In contrast, deep tendon reflexes may diminish and even disappear in coma, although pyramidal signs can still be observed. Rarely, transient focal neurological deficits can occur.[52] Seizures are very rarely reported in HE.[53-55] Extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony and slowness of speech, parkinsonian-like tremor, and dyskinesia with diminished voluntary movements, are common findings; in contrast, the presence of involuntary movements similar to tics or chorea occur rarely.[56] Asterixis or "flapping tremor" is often present in the early to middle stages of HE that precede stupor or coma and is, in actuality, not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers or the rhythmic squeezing of the examiner's fingers. However, asterixis can be observed in other areas, such as the feet, legs, arms, tongue, and eyelids. Asterixis is not pathognomonic of HE because it can be observed in other diseases[56] (e.g., uremia). Notably, the mental (either cognitive or behavioral) and motor signs of HE may not be expressed, or do not progress in parallel, in each individual, therefore producing difficulties in staging the severity of HE. Hepatic myelopathy (HM) is a particular pattern of HE possibly related to marked, long-standing portocaval shunting, characterized by severe motor abnormalities exceeding the mental dysfunction. Cases of paraplegia with progressive spasticity and weakness of lower limbs with hyper-reflexia and relatively mild persistent or recurrent mental alterations have been reported and do not respond to standard therapy, including ammonia lowering, but may reverse with liver transplantation (LT).[57] Persistent HE may present with prominent extrapyramidal and/or pyramidal signs, partially overlapping with HM, in which postmortem brain examination reveals brain atrophy. This

condition was previously called acquired hepatolenticular degeneration, a term currently considered obsolete. However, this cirrhosis-associated parkinsonism is unresponsive to ammonia-lowering therapy and may be more common than originally thought in patients with advanced liver disease, presenting in approximately 4% of cases.

Apart from these less-usual manifestations of HE, it is widely accepted in clinical practice that all forms of HE and their manifestations are completely reversible, and this assumption still is a well-founded operational basis for treatment strategies.

CLASSIFICATION

Hepatic encephalopathy should be classified according to all of the following four factors.10

1. **According to the underlying disease**, HE is subdivided into

• Type A resulting from ALF

• Type B resulting predominantly from portosystemic bypass or shunting

• Type C resulting from cirrhosis

The clinical manifestations of types B and C are similar, whereas type A has distinct features and, notably, may be associated with increased intracranial pressure and a risk of cerebral herniation.

2. **According to the severity of manifestations**. The continuum that is HE has been arbitrarily subdivided. For clinical and research purposes, a scheme of such grading is provided.

WHC INCLUDING MHE	ISHEN	DESCRIPTION	SUGGESTED OPERATIVE CRITERIA	COMMENT
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible

Grade II	overt	Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

Operative classifications that refer to defined functional impairments aim at increasing intra- and inter-rater reliability and should be used whenever possible.

3. **According to its time course**, HE is subdivided into

• Episodic HE

• Recurrent HE denotes bouts of HE that occur with a time interval of 6 months or less.

• Persistent HE denotes a pattern of behavioral alterations that are always present and interspersed with relapses of overt HE.

4**. According to the existence of precipitating factors**, HE is subdivided into

• Nonprecipitated

• Precipitated, and the precipitating factors should be specified.

Precipitating factors can be identified in nearly all bouts of episodic HE type C and should be actively sought and treated when found.

PRECIPITATING FACTORS FOR OHE BY DECREASING FREQUENCY

EPISODIC	**RECURRENT**
Infections	Electrolyte disorder
GI bleeding	Infection
Diuretic overdose	Unidentified
Electrolyte imbalance	Constipation
Constipation	Diuretic Overdose
Unidentified	GI bleeding

5.A fifth classification, according to whether or not the patient has acute-on-chronic liver failure (ACLF), has recently been suggested.[59] Although the management, mechanism, and prognostic impact differ, this classification is still a research area.

PATHOGENESIS

The two elements that confer the name to the syndrome and intervene in its clinical classification are neurological disturbance and liver failure. According to the characteristics of the neurological manifestations, HE is classified as episodic (previously acute), persistent (previously chronic), or minimal (previously subclinical).[60] Depending on the disease of the liver, HE is termed type C (associated with cirrhosis), type A (associated with acute liver failure), or type B (associated with portal-systemic bypass and no intrinsic liver disease). Irrespective of the characteristics of the neurological manifestations and the type of liver disease, the link between them is that HE is caused by the effects on the brain of substances that under normal circumstances are efficiently metabolized by the liver. Ammonia remains as the most important factor in the pathogenesis of HE. Currently, there is a better explanation of the mechanisms by which ammonia interferes with brain function and a better recognition of the factors that influence these effects.

Ammonia

The association between ammonia neurotoxicity and HE was first suggested by studies in dogs that underwent portal-cava anastomosis (Eck's fistula) and developed neurological manifestations when fed meat.[61] Ammonia is generated in the intestines from different sources: nitrogenous components of the diet, deamination of glutamine, and breakdown of urea by urease present in colonic flora. These features have been known for many years and have been the basis for designing treatments for HE based on the modulation of intestinal generation of ammonia (Fig. 1). Glutaminase, the enzyme that metabolizes the deamination of glutamine, has been thought to play an important role in the pathogenesis of HE.[62] In the intestines, the activity of glutaminase has been associated with minimal HE, probably because it

regulates the generation of ammonia.[63] Neomycin, a drug that improves HE, may act by inhibiting intestinal glutaminase. In the brain, glutaminase is located in the mitochondria of astrocytes and might be implicated in the toxic effects of ammonia in this organelle.[64] Interorgan ammonia trafficking has been quanti- fied in cirrhotic patients.[65] The relative contribution of different organs highlights the role of skeletal muscle to buffer ammonia that is produced in the intestines and is not metabolized in the liver. These data suggest that favoring an anabolic metabolic state may decrease ammonia concentration in the blood. A negative protein balance has been shown in advanced cirrhosis. This balance can be partially reversed in different clinical situations. Isoleucine infusions promote protein synthesis after gastrointestinal bleeding,[66] anabolic steroids improve nutritional status in moderately malnourished patients with acute alcoholic hepatitis, and a diet with normal protein content avoids the increased protein breakdown seen in patients with episodic HE treated with low-protein diets.[67] Malnourishment, which traditionally has been linked to a worse clinical outcome in cirrhosis, may be difficult to combat through diet interventions. Branched chain amino acids may be helpful for this purpose, because they promote protein synthesis.[68] The administration of branched chain amino acids-enriched diets may slow the progression of cirrhosis[69] and through this mechanism improve persistent HE. The kidney is another organ that is important in regulating blood ammonia levels. An increase in the generation of ammonia in the kidney has been shown after gastrointestinal bleeding[70] and may follow dehydration and the administration of diuretics. Expansion of plasma volume, a common practice in patients with episodic HE, increases the excretion of urea in the urine and may be helpful to shorten the duration of HE.[71] A common criticism of the role of ammonia in HE has been the lack of a good correlation between blood levels and the severity of

HE.[72] At physiological pH, blood ammonia is mostly ionized (NH4). Small changes in pH have effects in the equilibrium and affect the amount of un-ionized ammonia (NH3), which is the form that passes the blood-brain barrier by diffusion. In some studies, the correlation between arterial ammonia and HE has been improved after adjusting for pH,[73] but this has not been confirmed by other authors.[74] Part of the lack of association between plasma ammonia and HE can be accounted for by differences in ammonia concentration between blood and the central nervous system. This difference could be explained by differences in pH between the compartments and by the presence of active transporters. It has been estimated that at least 20% of ammonia may pass the blood-brain barrier ionized (NH4) through an active transport.[75] Cerebral blood flow and the permeability surface area are other elements that may determine the delivery of ammonia to the brain.

Inflammation

Apart from ammonia, there are other factors that appear to have an important role in the development of HE. This is apparent from the differences between HE in cirrhosis and other diseases that share high levels of ammonia but different clinical outcomes, such as inborn errors of metabolism or congenital portal-systemic shunts.[76]

In the latter, magnetic resonance studies and oral glutamine challenge tests have reproduced the same abnormalities as those present in cirrhosis.[77] However, episodic HE is very infrequent in patients with congenital shunts. One factor that may explain the development of episodic HE in cirrhosis is inflammation.[78] The presence of markers of a systemic inflammatory response has been linked to HE.[79] In patients with acute liver failure, it is well documented that the progression to severe HE is

associated with infection.[80] The exposition of astrocytes to cytokines in cultures induces astrocyte swelling, which is considered a neuropathological hallmark of HE.[81] In experimental models, lipopolysaccharide enhances ammonia-induced changes in cerebral hemodynamics.[82] For these reasons, it has been postulated that the inflammatory response may unlock the blood-brain barrier to the effects of toxins and may be responsible for most of the bouts of overt HE.[83] Interestingly, subclinical infection has been demonstrated among patients with advanced cirrhosis.[84]The induction of inflammatory response by these infections may cause those episodes of HE in which a precipitating event cannot be identified.

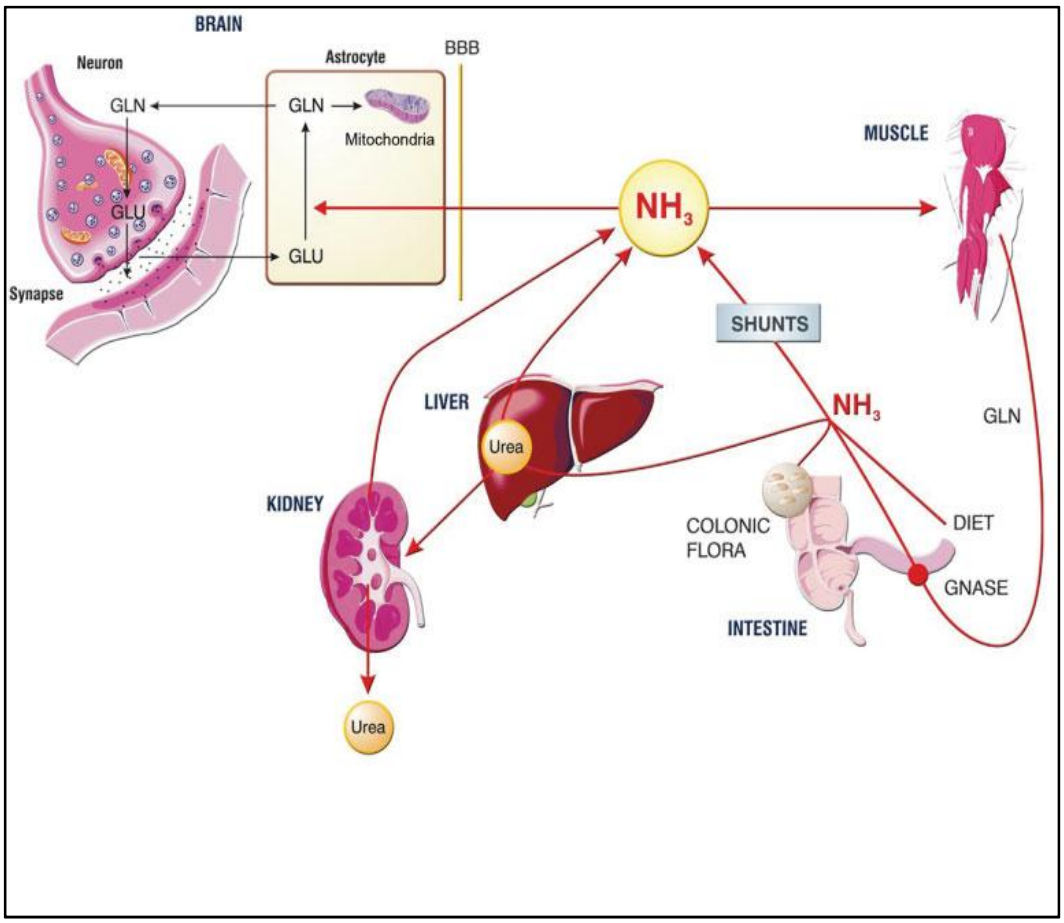


Figure 1: Interorgan ammonia trafficking and metabolism. Ammonia is generated in the intestines from nitrogenous compounds from the diet, deamination of glutamine by glutaminase, and metabolism of nitrogenous substances by colonic flora. In normal circumstances, most ammonia is metabolized to urea in the liver. Portal-systemic

shunts and liver failure cause a rise in blood ammonia that may affect brain function by inducing several disturbances in astrocytes; these may impair mitochondria and the glutamate-glutamine trafficking between neurons and astrocytes. Skeletal muscle is capable of decreasing blood ammonia by metabolizing ammonia to glutamine. The kidney has also an important role in determining blood ammonia by excreting urea in the urine and generating ammonia. NH3, ammonia; GLU, glutamate; GLN, glutamine; GNASE, glutaminase; BBB, blood-brain barrier.

Brain Disturbances

New technological advances have allowed a better knowledge of the disturbances present in the brain in HE, not only in experimental models, but also in patients with cirrhosis. Results of neuropathologic, spectroscopic, and neurochemical studies continue to indicate a major role for ammonia.[85] Although there is no unifying hypothesis, the molecular mechanisms of ammonia toxicity point at two important steps: (1) abnormalities in the metabolism of neurotransmitters and (2) neurotoxicity induced by oxidative stress. Glutamate is an amino acid that acts as an excitatory neurotransmitter and is present in presynaptic vesicles in more than 90% of the neurons. After its release and activation of different postsynaptic receptors, glutamate is removed from the synaptic cleft by transporters located at the astrocytes. In the astrocytes, glutamate is transformed into glutamine with the incorporation of one molecule of ammonia and transported into the presynaptic neuron, where glutamine will be transformed again into glutamate. This cycle is affected at several steps by ammonia, which has led to the proposal that impaired glutamatergic neurotransmission induces part of the neurological manifestations of HE. However, experimental attempts to modify these abnormalities have shown only marginal

amelioration. Another neurotransmitter system that is affected by ammonia is the inhibitory GABAergic neurotransmission. One of the mechanisms involved is the activation of neurosteroids, which are agonists of the g-aminobutyric acid (GABA) receptor and may be responsible for the inhibitory pattern of neuronal function that characterizes HE.[86] Ammonia has been shown to evoke oxidative stress inducing the generation of free radicals and the nitrotyrosination of proteins in the brain.[87] This process is critical for mitochondrial function and secondarily may cause failure of normal neurotransmission. Signs of impending energy failure have been shown in experimental models[88] and in patients with acute liver Figure 1 Interorgan ammonia trafficking and metabolism. Ammonia is generated in the intestines from nitrogenous compounds from the diet, deamination of glutamine by glutaminase, and metabolism of nitrogenous substances by colonic flora. In normal circumstances, most ammonia is metabolized to urea in the liver. Portal-systemic shunts and liver failure cause a rise in blood ammonia that may affect brain function by inducing several disturbances in astrocytes; these may impair mitochondria and the glutamate-glutamine trafficking between neurons and astrocytes. Skeletal muscle is capable of decreasing blood ammonia by metabolizing ammonia to glutamine. The kidney has also an important role in determining blood ammonia by excreting urea in the urine and generating ammonia. An additional effect of oxidative and nitrosative stress in astrocytes is the induction of swelling,[89] which has been consistently reproduced after exposure to ammonia. Astrocyte swelling can be exacerbated by some of the factors that precipitate HE, such as inflammatory mediators, hyponatremia, and benzodiazepines.[90] The change in the state of cellular hydration causes impairment of several metabolic pathways and has been suggested as being responsible for brain edema and for the neurological manifestations of HE.[91]

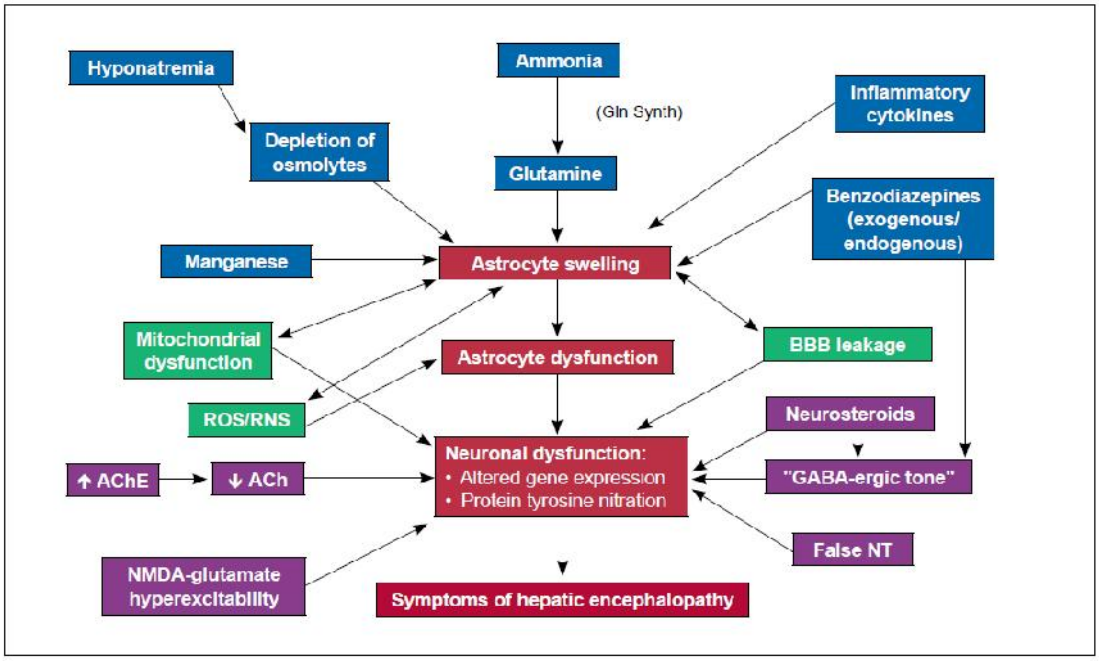


Figure 2 : Hypothesis of multi-factorial nature of HE

Differential Diagnosis of HE

The diagnosis requires the detection of signs suggestive of HE in a patient with severe liver insufficiencyand/or PSS who does not have obvious alternative causes of brain dysfunction. The recognition of precipitating factors for HE (e.g., infection, bleeding, and constipation) supports the diagnosis of HE. The differential diagnosis should consider common disorders altering the level of consciousness

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 Hyponatremia and sepsis can both produce encephalopathy per se and precipitate HE by interactions with the pathophysiological mechanisms. In endstage liver disease, uremic encephalopathy and HE may overlap.

management

1. Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

2. A diagnostic workup is required, considering other disorders that can alter brain function and mimic HE (GRADE II-2, A, 1).

Diagnosis and Testing

Clinical Evaluation

Judging and measuring the severity of HE is approached as a continuum.[92] The testing strategies in place range from simple clinical scales to sophisticated psychometric and neurophysiological tools; however, none of the current tests are valid for the entire spectrum. [93] The appropriate testing and diagnostic options differ according to the acuity of the presentation and the degree of impairment.[94]

Diagnosis and Testing for OHE

The diagnosis of OHE is based on a clinical examination and a clinical decision. Clinical scales are used to analyze its severity. Specific quantitative tests are only needed in study settings. The gold standard is the West Haven criteria (WHC; including clinical description). However, they are subjective tools with limited

interobserver reliability, especially for grade I HE, because slight hypokinesia, psychomotor slowing, and a lack of attention can easily be overlooked in clinical examination. In contrast, the detection of disorientation and asterixis has good inter-rater reliability and thus are chosen as marker symptoms of OHE.[94] Orientation or mixed scales have been used to distinguish the severity of HE.[95,96] In patients with significantly altered consciousness, the Glasgow Coma Scale (GCS) is widely employed and supplies an operative, robust description. Diagnosing cognitive dysfunction is not difficult. It can be established from clinical observation as well as neuropsychological or neurophysiological tests. The difficulty is to assign them to HE. For this reason, OHE still remains a diagnosis of exclusion in this patient population that is often susceptible to mental status abnormalities resulting from medications, alcohol abuse, drug use, effects of hyponatremia, and psychiatric disease. Therefore, as clinically indicated, exclusion of other etiologies by laboratory and radiological assessment for a patient with altered mental status in HE is warranted.

Testing for MHE and CHE

Minimal hepatic encephalopathy and CHE is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with CLD who are not disoriented or display asterixis. The term “minimal” conveys that there is no clinical sign, cognitive or other, of HE. The term “covert” includes minimal and grade 1 HE. Testing strategies can be divided into two major types: psychometric and neurophysiological. [97,98] Because the condition affects severalcomponents of cognitive functioning, which may not be impaired to the same degree, the ISHEN suggests the use of at least two tests, depending on the local population norms and availability, and preferably with one of the tests being more widely accepted so as to

serve as a comparator. Testing for MHE and CHE is important because it can prognosticate OHE development, indicate poor quality of life and reduced socioeconomic potential, and help counsel patients and caregivers about the disease. The occurrence of MHE and CHE in patients mwith CLD seems to be as high as 50%,[99] so, ideally, every patient at risk should be tested. However, this strategy may be costly,[100] and the consequences of the screening procedure are not always clear and treatment is not always recommended. An operational approach may be to test patients who have problems with their quality of life or in whom there are complaints from the patients and their relatives.[101] Tests positive for MHE or CHE before stopping HE drug therapy will identify patients at risk for recurrent HE.[102] Furthermore, none of the available tests are specific for the condition,[103] and it is important to test only patients who do not have confounding factors, such as neuropsychiatric disorders, psychoactive medication, or current alcohol use. Testing should be done by a trained examiner adhering to scripts that accompany the testing tools. If the test result is normal (i.e., negative for MHE or CHE), repeat testing in 6 months has been recommended. [104] A diagnosis of MHE or CHE does not automatically mean that the affected subject is a dangerous driver.[105] Medical providers are not trained to formally evaluate fitness to drive and are also not legal representatives. Therefore, providers should act in the best interests of both the patient and society while following the applicable local laws.[105] However, doctors cannot evade the responsibility of counseling patients with diagnosed HE on the possible dangerous consequences of their driving, and, often, the safest advice is to stop driving until the responsible driving authorities have formally cleared the patient for safe driving. In difficult cases, the doctor should consult with the authorities that have the expertise to test driving ability and the authority to revoke the license. A listing of

the most established testing strategies is given below. The test recommendation varies depending on the logistics, availability of tests, local norms, and cost.[92,93]

1. Portosystemic encephalopathy (PSE) syndrome test. This test battery consists of five paper-pencil tests that evaluate cognitive and psychomotor processing speed and visuomotor coordination. The tests are relatively easy to administer and have good external validity.[103] The test is often referred to as the Psychometric Hepatic Encephalopathy Score (PHES), with the latter being the sum score from all subtests of the battery. It can be obtained from Hannover Medical School (Hannover, Germany), which holds the copyright (Weissenborn.karin@mh-hannover. de). The test was developed in Germany and has been translated for use in many other countries. For illiterate patients, the figure connection test has been used as a subtest instead of the number connection test.[106]

2. The Critical Flicker Frequency (CFF) test is a psycho physiological tool defined as the frequency at which a fused light (presented from 60 Hz downward) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy. The CFF test requires several trials, intact binocular vision, absence of red-green blindness, and specialized equipment.[107,108]

3. The Continuous Reaction Time (CRT) test. The CRT test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most importanttest result is the CRT index, which measures the stability of the reaction times. The test result can differentiate between organic and metabolic brain impairment and is not influenced by the patient's age or gender, and there is no learning or tiring effect. Simple software and hardware are required.[109]

4. The Inhibitory Control Test (ICT) is a computerized test of response inhibition and working memory [110] and is freely downloadable at www.hecme.tv. The ICT test has

been judged to have good validity, but requires highly functional patients. The norms for the test have to be elaborated beyond the few centers that have used it.

5. The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a colored field and a written color name. Recently, mobile application software ("apps" for a smartphone or tablet computer) based on the test has been shown to identify cognitive dysfunction in cirrhosis compared to paper-pencil tests.[111] Further studies are under way to evaluate its potential for screening for MHE and CHE.

6. The SCAN Test is a computerized test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. The SCAN Test has been shown to be of prognostic value.[112]

7. Electroencephalography examination can detect changes in cortical cerebral activity across the spectrum of HE without patient cooperation or risk of a learning effect.[97] However, it is nonspecific and may be influenced by accompanying metabolic disturbances, such as hyponatremia as well as drugs. Possibly, the reliability of EEG analysis can increase with quantitative analysis. This specifically should include the background frequency with mean dominant frequency or spectral band analysis. Also, in most situations, EEG requires an institutional setup and neurological expertise in evaluation, and the cost varies among hospitals.

Although the above-described tests have been used to test for MHE and CHE, there is, most often, a poor correlation between them because HE is a multidimensional dysfunction.[113] Learning effect is often observed with psychometric tests and it is unclear whether current HE therapy plays a role in the test performance. Therefore, interpretation of these tests and consideration of the results for further management need an understanding of the patient's history, current therapy, and

effect on the patient's daily activities, if signs of HE are found. For multicenter studies, the diagnosis of MHE or CHE by consensus should utilize at least two of the current validated testing strategies: paper-pencil (PHES) and one of the following: computerized (CRT, ICT, SCAN, or Stroop) or neurophysiological (CFF or EEG).[93] In the clinical routine or single-center studies, investigators may use tests for assessing the severity of HE with which they are familiar, provided that normative reference data are available and the tests have been validated for use in this patient population.[93]

Laboratory Testing

High blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients with CLD.[114] However, in case an ammonia level is checked in a patient with OHE and it is normal, the diagnosis of HE is in question. For ammonia-lowering drugs, repeated measurements of ammonia may be helpful to test the efficacy. There may be logistic challenges to accurately measure blood ammonia, which should be taken into consideration. Ammonia is reported either in venous, arterial blood, or plasma ammonia, so the relevant normal should be used. Multiple methods are available, but measurements should only be employed when laboratory standards allow for reliable analyses.

Brain Scans

Computed tomography (CT) or magnetic resonance (MRI) or other image modality scans do not contribute diagnostic or grading information. However, the risk of intracerebral hemorrhage is at least 5-fold increased in this patient group,[115] and the symptoms may be indistinguishable, so a brain scan is usually part of the diagnostic workup of first-time HE and on clinical suspicion of other pathology.

TREATMENT

General Principles

At this time, only OHE is routinely treated. Minimal hepatic encephalopathy and CHE, as its title implies, is not obvious on routine clinical examination and is predominantly diagnosed by techniques outlined in the previous section. Despite its subtle nature, MHE and CHE can have a significant effect on a patient's daily living. Special circumstances can prevail where there may be an indication to treat such a patient (e.g., impairment in driving skills, work performance, quality of life, or cognitive complaints). Liver transplantation is mentioned under the treatment recommendations. Comments on Management Strategy Patients with higher grades of HE who are at risk or unable to protect their airway need more intensive monitoring and are ideally managed in an intensive care setting. Alternative causes of encephalopathy are not infrequent in patients with advanced cirrhosis. Technically, if other causes of encephalopathy are present, then the episode of encephalopathy may not be termed HE. In the clinical setting, what transpires is treatment of both HE and non-HE. Controlling precipitating factors in the management of OHE is of paramount importance, because nearly 90% of patients can be treated with just correction of the precipitating factor.[116] Careful attention to this issue is still the cornerstone of HE management.

Therapy for Episodes of OHE

In addition to the other elements of the fourpronged approach to treatment of HE, specific drug treatment is part of the management. Most drugs have not been tested by rigorous randomized, controlled studies and are utilized based on circumstantial observations. These agents include nonabsorbable disaccharides, such as lactulose, and antibiotics, such as rifaximin. Other therapies, such as oral branched-

chain amino acids (BCAAs), intravenous (IV) L-ornithine Laspartate (LOLA), probiotics, and other antibiotics, have also been used. In the hospital, a nasogastric tube can be used to administer oral therapies in patients who are unable to swallow or have an aspiration risk. Nonabsorbable Disaccharides. Lactulose is generally used as initial treatment for OHE. A large metaanalysis of trial data did not completely support lactulose as a therapeutic agent for treatment of OHE, but for technical reasons, it did not include the largest trials, and these agents continue to be used widely.[117] Lack of effect of lactulose should prompt a clinical search for unrecognized precipitating factors and competing causes for the brain impairment. Though it is assumed that the prebiotic effects (the drug being a nondigestible substance that promotes the growth of beneficial microorganisms in the intestines) and acidifying nature of lactulose have an additional benefit beyond the laxative effect, culture-independent studies have not borne those out.[102,118] In addition, most recent trials on lactulose have been open label in nature. Cost considerations alone add to the argument in support of lactulose.[119] In some centers, lactitol is preferred to lactulose, based on small meta-analyses of even smaller trials.[120,121] In populations with a high prevalence of lactose intolerance, the use of lactose has been suggested.[122]However, the only trial to show that stool acidifying enemas (lactose and lactulose) were superior to tap water enemas was underpowered.[123] The use of polyethylene glycol preparation[124] needs further validation. The dosing of lactulose should be initiated[125] when the three first elements of the four-pronged approach are completed, with 25mL of lactulose syrup every 1-2 hours until at least two soft or loose bowel movements per day are produced. Subsequently, the dosing is titrated to maintain two to three bowel movements per day. This dose reduction should be implemented. It is a misconception that lack of effect of smaller amounts of lactulose is remedied by much

larger doses. There is a danger for overuse of lactulose leading to complications, such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation, and overuse can even precipitate HE.[126]

Rifaximin

Rifaximin has been used for the therapy of HE in a number of trials[127] comparing it with placebo, other antibiotics, nonabsorbable disaccharides, and in dose-ranging studies. These trials showed effect of rifaximin that was equivalent or superior to the compared agents with good tolerability. Long-term cyclical therapy over 3-6 months with rifaximin for patients with OHE has also been studied in three trials (two compared to nonabsorbable disaccharides and one against neomycin) showing equivalence in cognitive improvement and ammonia lowering. A multinational study[128] with patients having two earlier OHE bouts to maintain remission showed the superiority of rifaximin versus placebo (in the background of 91% lactulose use). No solid data support the use of rifaximin alone. Other Therapies. Many drugs have been used for treatment of HE, but data to support their use are limited, preliminary, or lacking. However, most of these drugs can safely be used despite their limited proven efficacy.

BCAAs.

An updated meta-analysis of eight randomized, controlled trials (RCTs) indicated that oral BCAA-enriched formulations improve the manifestations of episodic HE whether OHE or MHE.[129] There is no effect of IV BCAA on the episodic bout of HE.

Metabolic Ammonia Scavengers.

These agents, through their metabolism, act as urea surrogates excreted in urine. Such drugs have been used for treatment of inborn errors of the urea cycle for

many years. Different forms are available and currently present as promising investigational agents. Ornithine phenylacetate has been studied for HE, but further clinical reports are awaited.[130] Glyceryl phenylbutyrate (GPB) was tested in a recent RCT[131] on patients who had experienced two or more episodes of HE in the last 6 months and who were maintained on standard therapy (lactulose 6 rifaximin). The GPB arm experienced fewer episodes of HE and hospitalizations as well as longer time to first event. More clinical studies on the same principle are under way and, if confirmed, may lead to clinical recommendations. L-ornithine L-aspartate (LOLA). An RCT on patients with persistent HE demonstrated improvement by IV LOLA in psychometric testing and postprandial venous ammonia levels.[132] Oral supplementation with LOLA is ineffective.

Probiotics.

A recent, open-label study of either lactulose,probiotics, or no therapy in patients with cirrhosis who recovered from HE found fewer episodes of HE in the lactulose or probiotic arms, compared to placebo, but were not different between either interventions. There was no difference in rates of readmission in any of the arms of the study.[133]

Glutaminase Inhibitors.

Portosystemic shunting up-regulates the intestinal glutaminase gene so that intestinal glutaminase inhibitors may be useful by reducing the amounts of ammonia produced by the gut. Neomycin. This antibiotic still has its advocates and was widely used in the past for HE treatment; it is a known glutaminase inhibitor.[134]

Metronidazole.

As short-term therapy,[135] metronidazole also has advocates for its use. However, longterm ototoxicity, nephrotoxicity, and neurotoxicity make these agents unattractive for continuous long-term use.

Flumazenil.

This drug is not frequently used. It transiently improves mental status in OHE without improvement on recovery or survival. The effect may be of importance in marginal situations to avoid assisted ventilation. Likewise, the effect may be helpful in difficult differential diagnostic situations by confirming reversibility (e.g., when standard therapy unexpectedly fails or when benzodiazepine toxicity is suspected).

Laxatives.

Simple laxatives alone do not have the prebiotic properties of disaccharides, and no publications have been forthcoming on this issue.

Albumin.

A recent RCT on OHE patients on rifaximin given daily IV albumin or saline showed no effect on resolution of HE, but was related to better postdischarge survival.[136]Prevention of Overt Hepatic Encephalopathy After an Episode of OHE. There are no randomized, placebo-controlled trials of lactulose for maintenance of remission from OHE. However, it is still widely recommended and practiced. A single-center, open-label RCT of lactulose demonstrated less recurrence of HE in patients with cirrhosis. A recent RCT supports lactulose as prevention of HE subsequent to upper gastrointestinal (GI) bleeding.[137] Rifaximin added to lactulose is

the best-documented agent to maintain remission in patients who have already experienced one or more bouts of OHE while on lactulose treatment after their initial episode of OHE.[128]

Hepatic Encephalopathy After TIPS.

Once TIPS was popularized to treat complications of PH, its tendency to cause the appearance of HE, or less commonly, intractable persistent HE, was noted. Faced with severe HE as a complication of a TIPS procedure, physicians had a major dilemma. Initially, it was routine to use standard HE treatment to prevent post-TIPS HE. However, one study illustrated that neither rifaximin nor lactulose prevented post-TIPS HE any better than placebo.[138] Careful case selection has reduced the incidence of severe HE post-TIPS. If it occurs, shunt diameter reduction can reverse HE.[139] However, the original cause for placing TIPS may reappear. Another important issue with TIPS relates to the desired portal pressure (PP) attained after placement of stents. Too low a pressure because of large stent diameter can lead to intractable HE, as noted above. There is a lack of consensus on whether to aim to reduce PP

by 50% or below 12 mmHg. The latter is associated with more bouts of encephalopathy.[140] It is widely used to treat post-TIPS recurrent HE as with other cases of recurrent HE, including the cases that cannot be managed by reduction of shunt diameter.

Hepatic Encephalopathy Secondary to Portosystemic Shunts (PSSs).

Recurrent bouts of overt HE in patients with preserved liver function consideration should lead to a search for large spontaneous PSSs. Certain types of shunts, such as splenorenal shunts, can be successfully embolized with rapid clearance of overt HE in

a fraction of patients in a good liver function status, despite the risk for subsequent VB.[141]

Discontinuation of Prophylactic Therapy. There is a nearly uniform policy to continue treatment indefinitely after it has successfully reversed a bout of OHE. The concept may be that once the thresholds for OHE is reached, then patients are at high risk for recurrent episodes. This risk appears to worsen as liver function deteriorates. However, what often occurs are recurrent bouts of OHE from a well-known list of precipitating factors. If a recurrent precipitating factor can be controlled, such as recurrent infections or variceal hemorrhages, then HE recurrence may not be a risk and HE therapy can be discontinued. Even more influential on the risk for further bouts of OHE is overall liver function and body habitus. If patients recover a significant amount of liver function and muscle mass from the time they had bouts of OHE, they may well be able to stop standard HE therapy. There are very little data on this issue, but tests positive for MHE or CHE before stopping HE drug therapy will predict patients at risk for recurrent HE.

Treatment of Minimal HE and Covert HE

Although it is not standard to offer therapy for MHE and CHE, studies have been performed using several modes of therapy. The majority of studies have been for less than 6 months and do not reflect the overall course of the condition. Trials span the gamut from small open-label trials to larger, randomized, controlled studies using treatments varying from probiotics, lactulose, and rifaximin. Most studies have shown an improvement in the underlying cognitive status, but the mode of diagnosis has varied considerably among studies. A minority of studies used clinically relevant

endpoints. It was shown, in an open-label study,[142] that lactulose can prevent development of the first episode of OHE, but the study needs to be replicated in a larger study in a blinded fashion before firm recommendations can be made. Studies using lactulose and rifaximin have shown improvement in quality of life,[143] and also in driving simulator performance.[144] Probiotics have also been used, but the open-label nature, varying amounts and types of organisms, and different outcomes make them difficult to recommend as therapeutic options at this time.[145-148] Because of the multiple methods used to define MHE and CHE, varying endpoints, short-term treatment trials, and differing agents used in trials to date, routine treatment for MHE is not recommended at this stage. Exceptions could be made on a case-by-case basis using treatments that are approved for OHE, particularly for patients with CHE and West Haven Grade I HE.

Nutritional Recommendations:[149-153]

1. Daily energy intakes should be 35-40 kcal/kg ideal body weight (GRADE I, A, 1).

2. Daily protein intake should be 1.2-1.5 g/kg/ day (GRADE I, A, 1).

3. Small meals or liquid nutritional supplements evenly distributed throughout the day and a latenight snack should be offered (GRADE I, A, 1).

4. Oral BCAA supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein (GRADE II-2, B, 2).

Follow-up

After a hospital admission for HE, the following issues should be addressed.

Discharge From Hospital

1. The medical team should confirm the neurological status before discharge and judge to what extent the patient's neurological deficits could be attributable to HE, or

to other neurological comorbidities, for appropriate discharge planning. They should inform caregivers that the neurological status may change once the acute illness has settled and that requirement for medication could change.

2. Precipitating and risk factors for development of HE should be recognized. Future clinical management should be planned according to (1) potential for improvement of liver function (e.g., acute alcoholic hepatitis, autoimmune hepatitis, and hepatitis B), (2) presence of large portosystemic shunts (which may be suitable for occlusion), and (3) characteristics of precipitating factors (e.g., prevention of infection, avoidance of recurrent GI bleeding, diuretics, or constipation).

3. Out-patient postdischarge consultations should be planned to adjust treatment and prevent the reappearance of precipitating factors. Close liaison should be made with the patient's family, the general practitioner, and other caregivers in the primary health service, so that all parties involved understand how to manage HE in the specific patient and prevent repeated hospitalizations.

Preventive Care After Discharge

1. *Education of patients and relatives should include* (1) effects of medication (lactulose, rifaximin, and so on) and the potential side effects (e.g., diarrhea), (2) importance of adherence, (3) early signs of recurring HE, and (4) actions to be taken if recurrence (e.g., anticonstipation measures for mild recurrence and referral to general practitioner or hospital if HE with fever).

2. *Prevention of recurrence*: the underlying liver pathology may improve with time, nutrition, or specific measures, but usually patients who have developed OHE have advanced liver failure without much hope for functional improvements and are often potential LT candidates. Managing the complications of cirrhosis (e.g., spontaneous

bacterial peritonitis and GI bleeding) should be instituted according to available guidelines. Pharmacological secondary prevention is mentioned above.

3. Monitoring neurological manifestations is necessary in patients with persisting HE to adjust treatment and in patients with previous HE to investigate the presence and degree of MHE or CHE or signs of recurring HE. The cognitive assessment depends on the available normative data and local resources. The motor assessment should include evaluation of gait and walking and consider the risk of falls.

4. The socioeconomic implications of persisting HE or MHE or CHE may be very profound. They include a decline in work performance, impairment in quality of life, and increase in the risk of accidents. These patients often require economic support and extensive care from the public social support system and may include their relatives. All these issues should be incorporated into the follow-up plan.

5. Treatment endpoints depend on the monitoring used and the specialist clinic, but at least they have to cover two aspects: (1) cognitive performance (improvement in one accepted test as a minimum) and (2) daily life autonomy (basic and operational abilities).

6. Nutritional aspects: weight loss with sarcopenia may worsen HE, and, accordingly, the nutritional priority is to provide enough protein and energy to favor a positive nitrogen balance and increase in muscle mass, as recommended above.

7. Portosystemic shunt: occlusion of a dominant shunt may improve HE in patients with recurring HE and good liver function.[141]Because the current experience is limited, the risks and benefits must be weighed before employing this strategy.

METHODOLOGY

3.1 Study design:

This study aimed to find out Precipitating factors for Hepatic Encephalopathy in Cirrhosis of Liver at KLES DR PRABHAKAR KORE HOSPITAL. A cross sectional study design was used to conduct the study.

3.2 Study site and area:

Data was collected from the patients presenting to Department of Internal medicine at KLES Dr Prabhakar Kore Hospital & MRC, Belgaum fulfilling inclusion criteria.

Duration of study: One year

Period of study: January 2015 to Dec 2015

3.3 Method of the Collection of the Data

Patients admitted with hepatic encephalopathy with cirrhosis of liver will be subjected to detailed history, examination and processed through necessary investigations with informed consent

Sample size: 84

sample size calculation $4pq/d^2$ (prevalence of HE in CL at any given time is 30 to 45 %[1,2]) absolute error 10%

3.5 Sample selection criteria:

3.5.1 Inclusion criteria:

All cases of cirrhosis of liver with hepatic encephelopathy

3.5.2 Exclusion criteria:

EXCLUSION CRITERIA:

1) Age<18 years
2) Metabolic disorders with encephelopathies
3) Encephalitis
4) Degenerative neurological diseases
5) Cerebrovascular accident
6) Intra-cerebral space occupying lesions

3.6 Procedure of data collection:

1)All the patients fulfilling the inclusion criteria and willing to participate, will be included in the study.

2)Informed consent will be obtained. If in any case patient is unconscious or disoriented consent will be obtained from authorised legal representative.

3)Further they will be subjected to a detailed history, clinical examination, investigations and imaging as in predesigned proforma.

4) Data will be analysed and tabulated for etiological profile of the patients.

At very beginning it was clarified that the participant had the right to refuse to answer of any question during completing questionnaire. They could withdraw from the study at any time. It was also clarified to all participants about the aim of the study. Participants were ensured that any personal information would not be published anywhere. After taking consent form the participants, they are subjected to a detailed history, clinical examination, laboratory investigations and imaging where ever required.

As this is a study of precipitating factors for HE in CL patients are not oriented to time and person with irrelevent speech in most of the patients where patients attender becomes the informant . All the data were collected by the researcher own to avoid the errors.

3.8 Field test:

Prior to collect data a field test was performed with 10 participants in the KLES Dr Prabhakar Kore Hospital. To make a feasible questionnaire was translated into kannada, Marathi and hindi. This test was performed to determine any difficulties that are exist in the questionnaires as well as the procedure of data collection. This test also helped the researcher to check the appropriateness of wording as well as ease of understanding of the questions and diagnosing a precipitating factor for HE.

3.9 Data analysis:

Descriptive statistics was used to analyze data. Descriptive statistics refers methods of describing a set of results in terms of their most interesting characteristics . Data were analyzed with the software named Statistical Package for the Social Science (SPSS) version 16.0. The variables were labeled in a list and established a computer based data definition record file that consist of a list of variables in order,

put the name of the variables in the variable view of SPSS and defined the types, values, decimal, label alignment and measurement level of data. The next step was cleaning new data files to check the inputted data set to ensure that all data had been accurately transcribed from the questionnaire sheet to the SPSS data view. Then the raw data was ready for analysis in SPSS. Data was analyzed by descriptive statistics and calculated as percentages and presented by using table, bar graph etc. Microsoft office Excel 2007 is used to decorating the bar graph.

3.10 Ethical consideration:

Ethical committee clearance was taken before starting the study. During the course of this study, interested subjects were given consent forms and the purpose of the research and the consent form were explained to them verbally in Kannada, Marathi or Hindi. The participants were informed that their participation would be fully voluntary and they had the right to withdraw or discontinue from the research at any time without any hesitation or risk. They were also informed that confidentiality would be maintained. Information might be published in any presentations or writing, but their personal identity such as their name and address will not be mention in the study. The participants were informed that the data was collected by written questionnaire. The supervisor also checked the consent form and questionnaire. For this study took permission during interview from every single participant with signature or thumb impression on a written consent form of the participants who were interested. The participants were informed about their role in the research process. The participants were informed about the aim of the research and procedures involved in the study. They were also informed that if they wish they were free to withdraw from the study any time. The study information only discusses with supervisor but

this would not share with any other person. These materials were disposed off after completion of the research project. The study results might not have any direct effects on them. Participants were also informed that they would not get any harmful things from the study.

3.11 Limitations

Despite best efforts with research, the present study was not completely free from all limitation and impediments. Limitations are:

- Sample size was small to generalize the study result.
- This study was done in a short period, so all factors in relation to precipitating factors for HE in CL cannot be studied
- Study was conducted only in KLE Dr PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE. So this study result would not be generalized for whole INDIA.
- To identify specifically that this is the only precipitating factor of HE in a given patient cannot be confirmed. This can be limitation of this study.
- Time and resources are limited have a great deal of impact on the study.

RESULTS

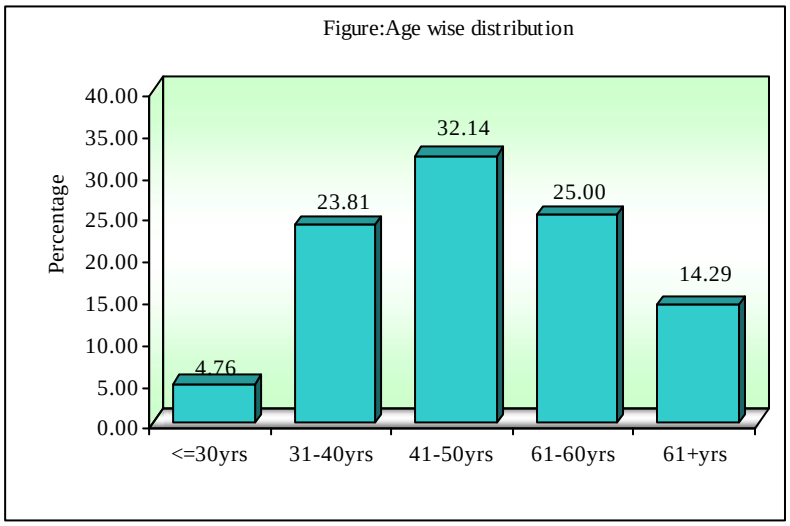
This study was conducted in KLES DR PRABHAKAR KORE HOSPITAL between January 2015 to December 2015.

4.1 AGE GROUP

The distribution of the subjects into the age group was as follows:

Table1: Age wise distribution

Age groups	No of patients	% of patients
<=30yrs	4	4.76
31-40yrs	20	23.81
41-50yrs	27	32.14
51-60yrs	21	25.00
61+yrs	12	14.29
Total	84	100.00
Mean age	47.95	
SD age	11.14	



Graph:1 A total of 84 patients have participated. There are maximum number of patients in age group of 31-60 years 80.95% (68).

Table2: Distribution of patients by gender

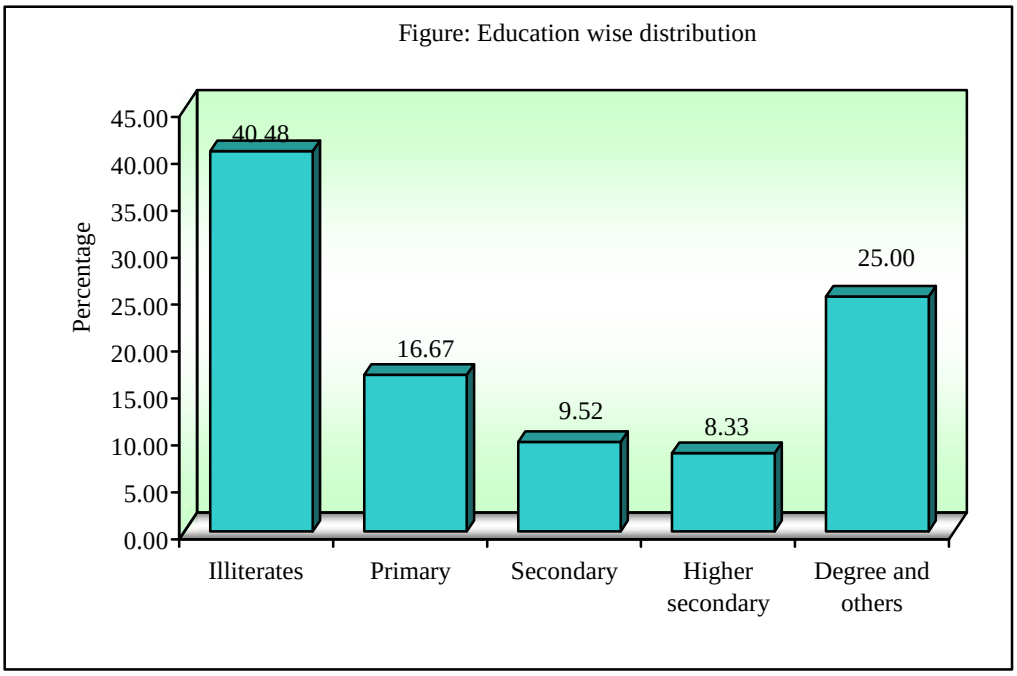
GENDER	NUMBER OF PATIENTS	PERCENTAGE OF PATIENTS
Male	81	96.43%
Female	3	3.57%
Total	84	100%

Out of 84 patients of HE 96.43%(81) patients are male patients.

Table3: Education wise distribution

Education	No of patients	% of patients
Illiterates	34	40.48
Primary	14	16.67
Secondary	8	9.52
Higher secondary	7	8.33
Degree and others	21	25.00
Total	84	100.00

Figure: Education wise distribution



Graph 2 According to level of education 40.48%(34) patients were illiterates.

Table 4: Precipitating factors for hepatic encephalopathy in order of frequency

Precipitating factors for HE	**Number of patients**	**Percentage**
Infection	35	41.67%
Upper GI bleeding	27	32.14%
Hyponatraemia	14	16.67%
Hepatorenal syndrome	10	11.90%
Hyperkalemia	9	10.71%
hypomagnesemia	7	8.33%
constipation	4	4.76%

Infection 41.67%(35) is the most common precipitating factor for HE.

Electrolyte imbalance seen in 34.52%(29) patients.

32.14%(27) patients had upper GI bleeding.

Hepatorenal syndrome is seen in 11.90%(10) patients.

Constipation is seen in 4.76%(4) patients.

Table 5: Spontaneous bacterial peritonitis as a precipitating factor

Spontaneous bacterial peritonitis	No of patients	% of patients
Absent	66	78.57
Present	18	21.43
Total	84	100.00

Figure: Spontaneous bacterial peritonitis wise distribution

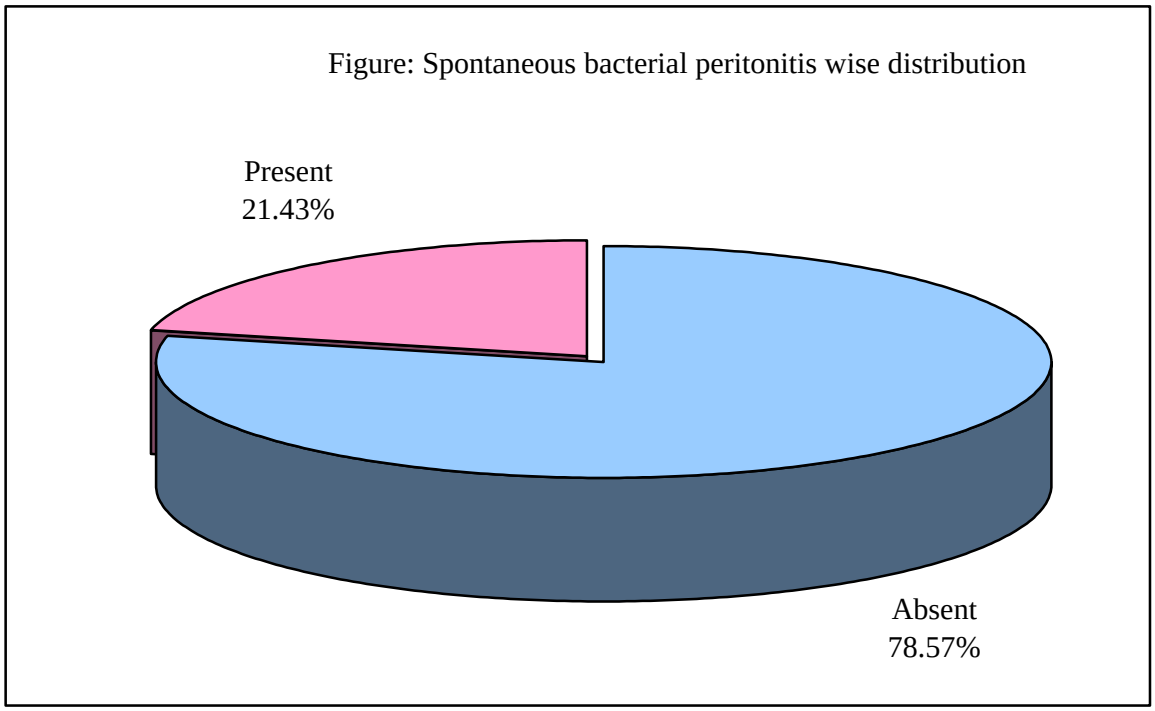


Figure 3 In this study ,spontaneous bacterial peritonitis is present in 21.43%(18) patients of HE .

Table :6 HE caused by other infections (cellulitis, pneumonia, acute gastroenteritis etc)

Other Infection	No of patients	% of patients
Absent	67	79.76
Present	17	20.24
Total	84	100.00

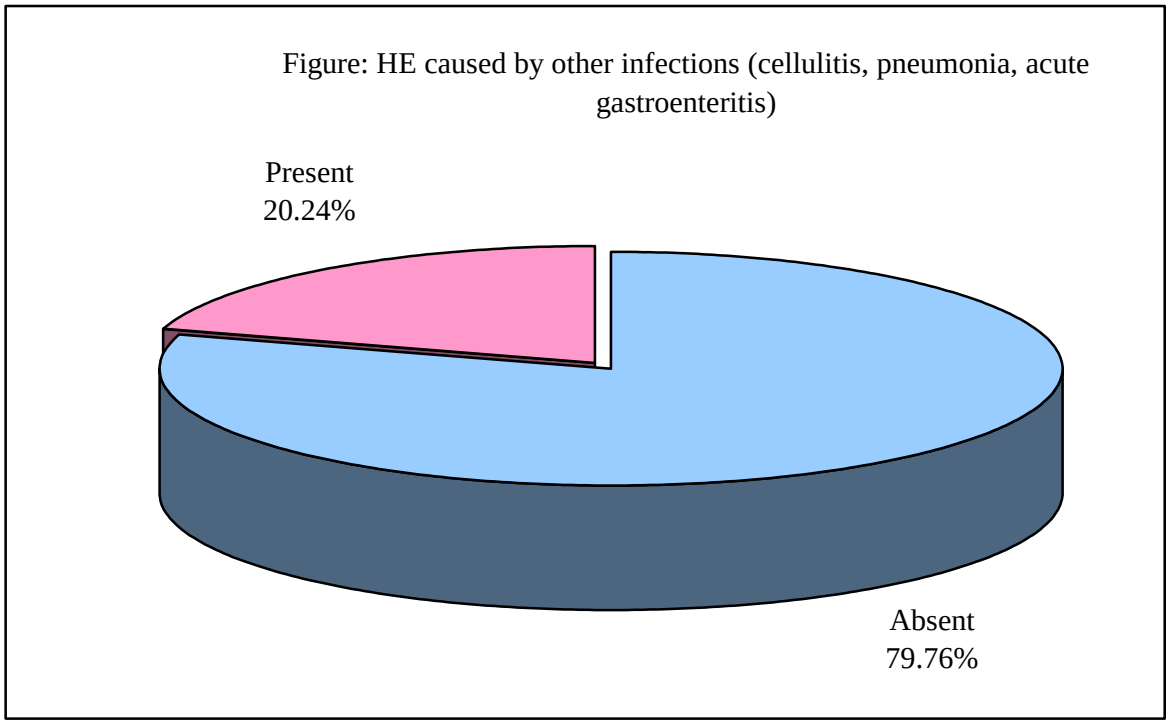


Figure 4 In this study other infections 20.24%(17) is cause for HE.

Table:7 Upper GI bleeding as a precipitating factor

Upper GI bleeding	No of patients	% of patients
Absent	57	67.86
Present	27	32.14
Total	84	100.00

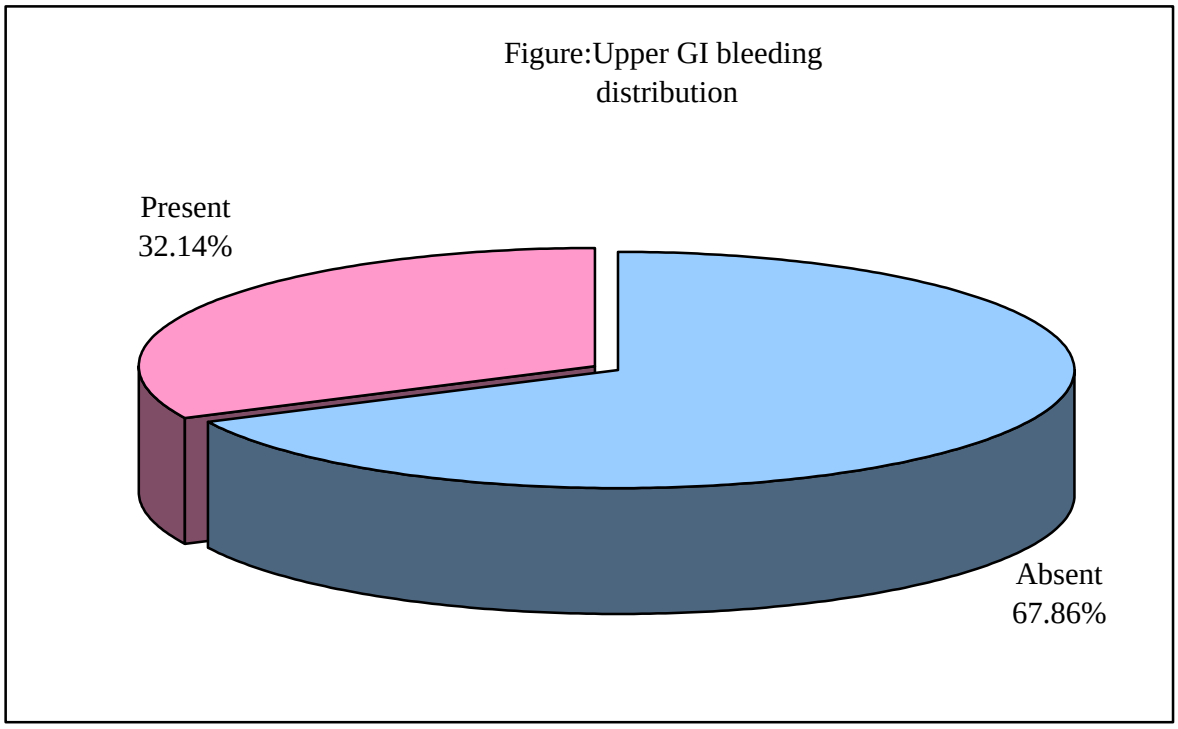


Figure 5 In this study upper GI bleed is present in 32.14%(27) of patients of HE.

Table: 8 Hyponatraemia as a precipitating factor

Hyponatraemia	No of patients	% of patients
Absent	70	83.33
Present	14	16.67
Total	84	100.00

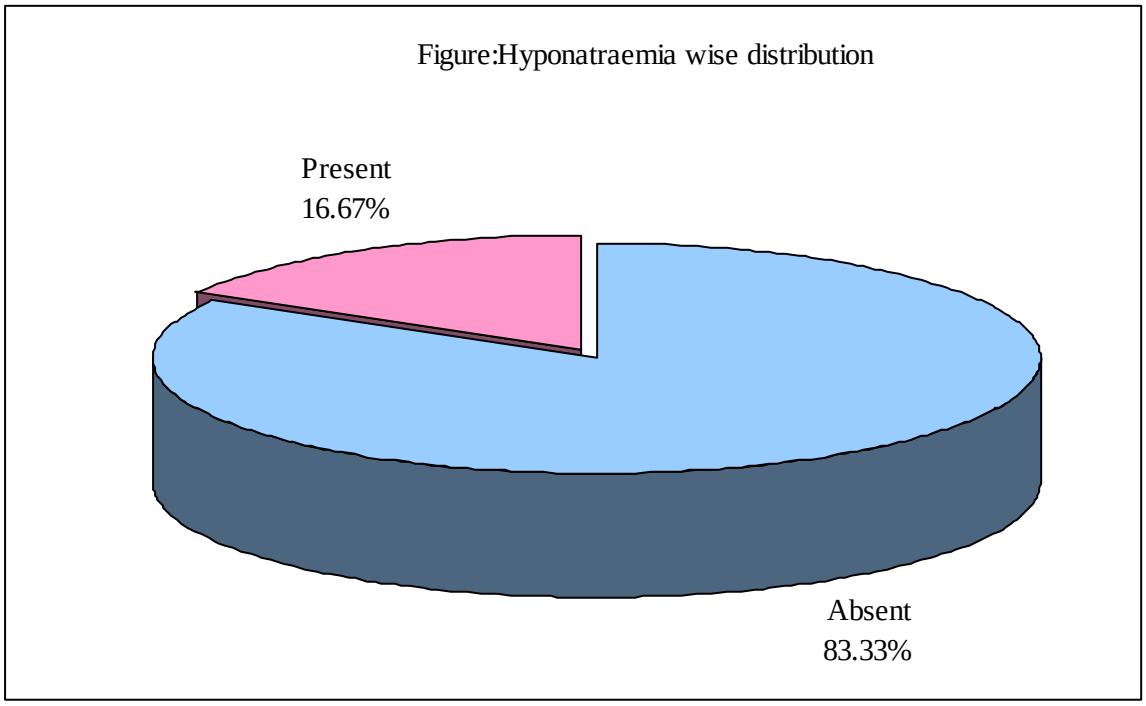


Figure 6: In 84 patients of HE hyponatremia was present in 16.67%(14) patients

Table:9 Hepatorenal syndrome as a precipitating factor

Hepatorenal syndrome	No of patients	% of patients
Absent	74	88.10
Present	10	11.90
Total	84	100.00

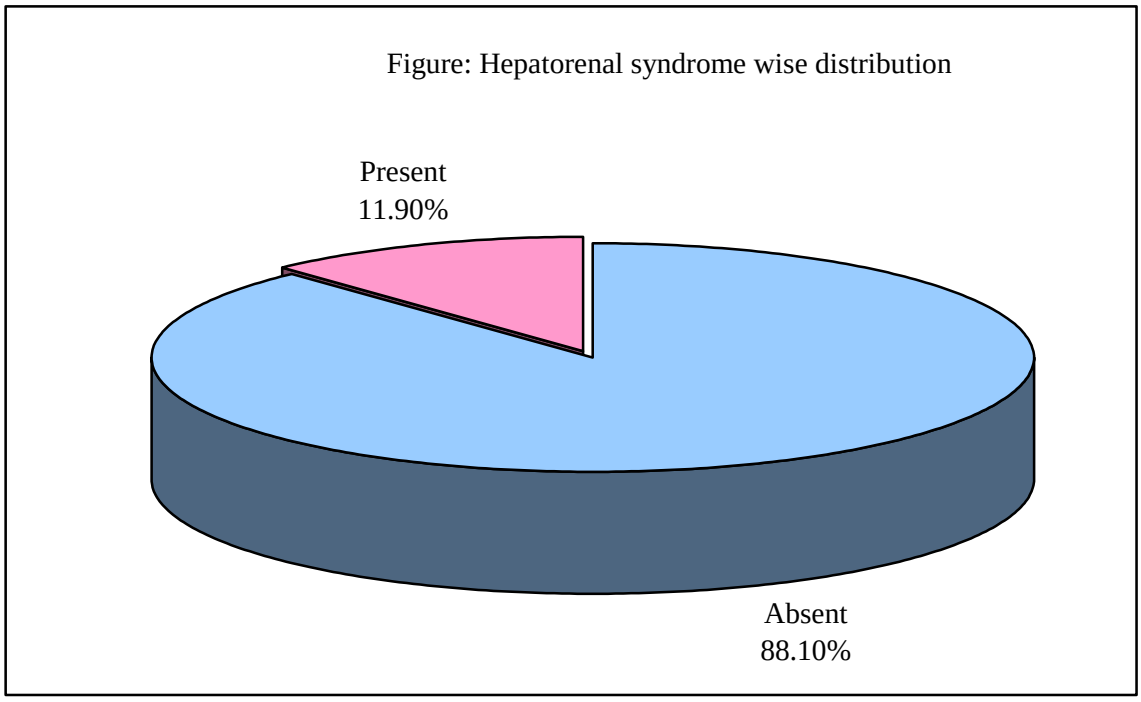


Figure 7 In 84 patients of hepatic encephalopathy,11.90%(10) patients have hepatorenal syndrome.

Table:10 Hyperkalaemia as a precipitating factor

Hyperkalaemia	No of patients	% of patients
Absent	75	89.29
Present	9	10.71
Total	84	100.00

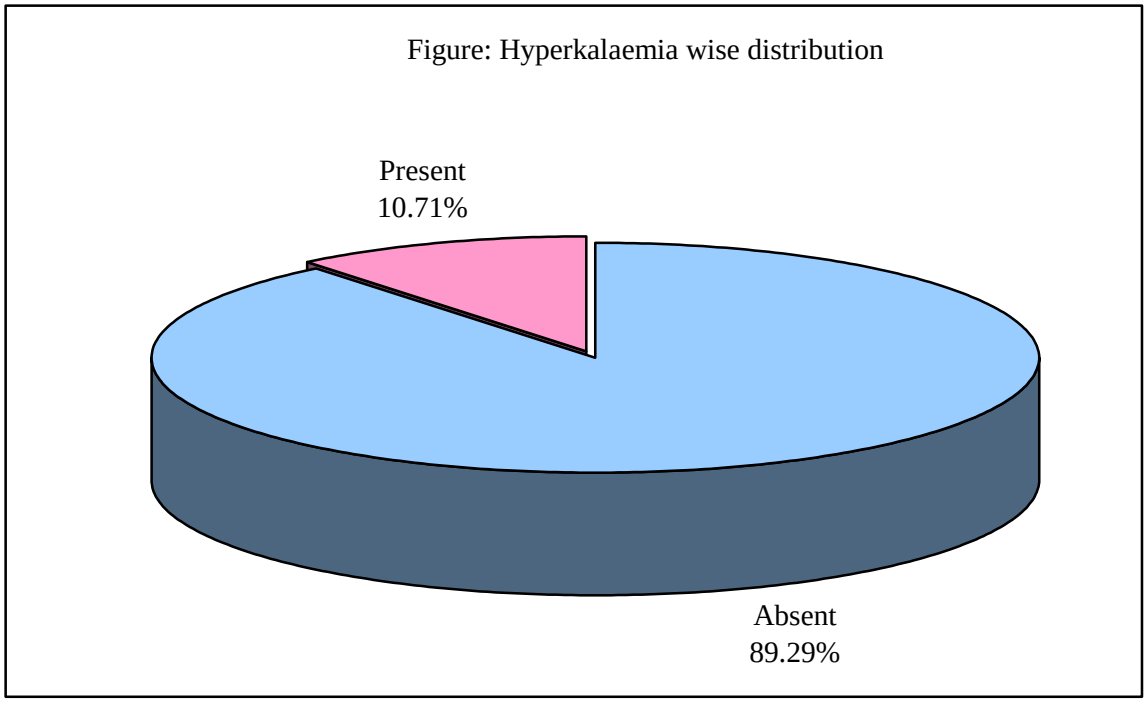


Figure 8 In this study hyperkalemia was seen in 10.71%(9) of patients with HE.

Table:11 Hypomagnesemia as a precipitating factor

Hypomagnesemia	No of patients	% of patients
Absent	77	91.67
Present	7	8.33
Total	84	100.00

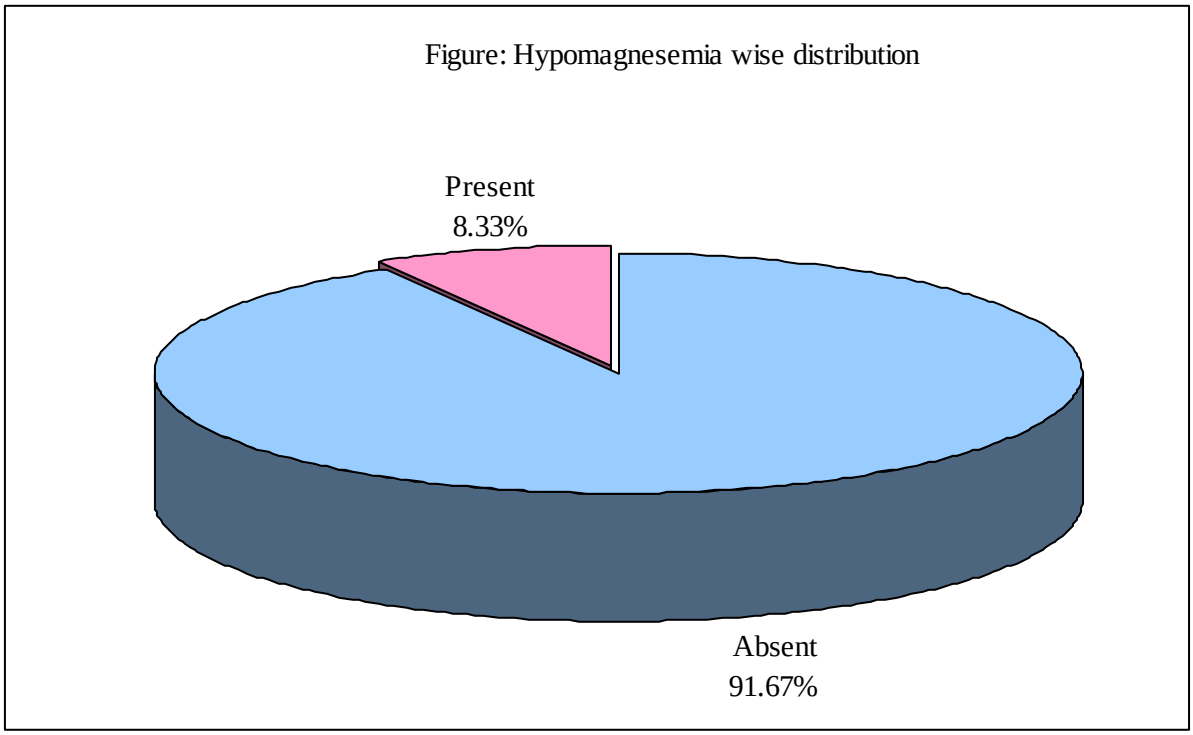


Figure 9 In this study , hypomagnaesemia is seen in 8.33%(7) patients.

Table:12 Constipation as a precipitating factor

Constipation	No of patients	% of patients
Absent	80	95.24
Present	4	4.76
Total	84	100.00

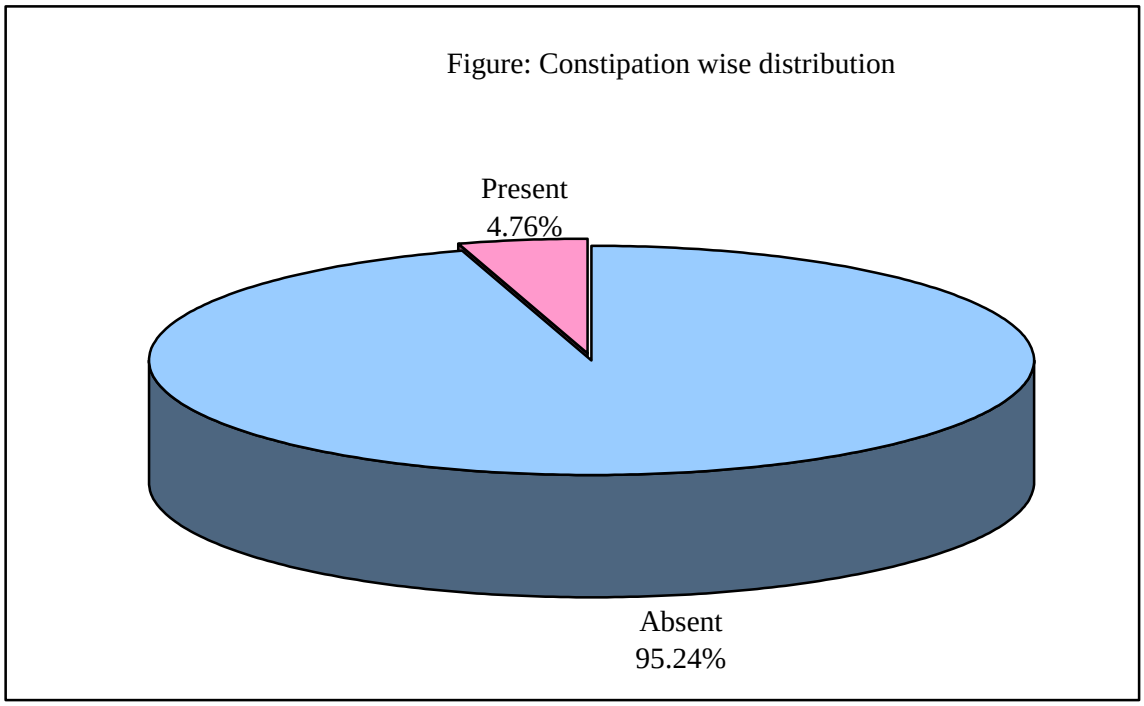


Figure 10 In this study 4.76%(4) of patients had HE secondary to constipation.

Table:13 HE grades wise distribution

HE grades	No of patients	% of patients
Grade I	2	2.38
Grade II	49	58.33
Grade III	29	34.52
Grade IV	4	4.76
Total	84	100.00

Figure:HE grades wise distribution

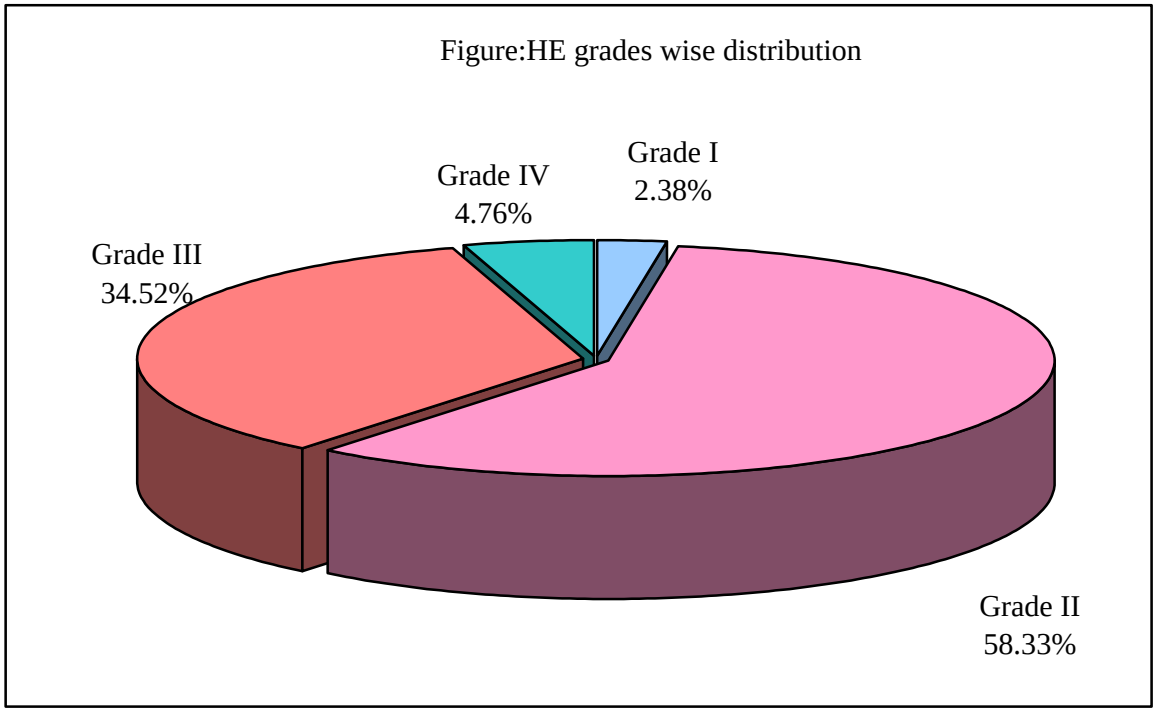


Figure 11 Among the participants (N=84) about 58.33% of patients have grade II hepatic encephelopathy, 34.52% have grade III HE, 4.76%(4) have grade IVHE and 2.38%(2) have grade I HE.

Table:14 Association between single and multi precipitating factors with HE grade

HE grade	Single precipitating factor	%	Multiple precipitating factors	%	Total	
Grade I	1	50.00	1	50.00	2	2.38
Grade II	41	83.67	8	16.33	49	58.33
Grade III	19	65.52	10	34.48	29	34.52
Grade IV	4	100.00	0	0.00	4	4.76
Total	65	77.38	19	22.62	84	100.00
Chi-square=4.2221 P = 0.1212						

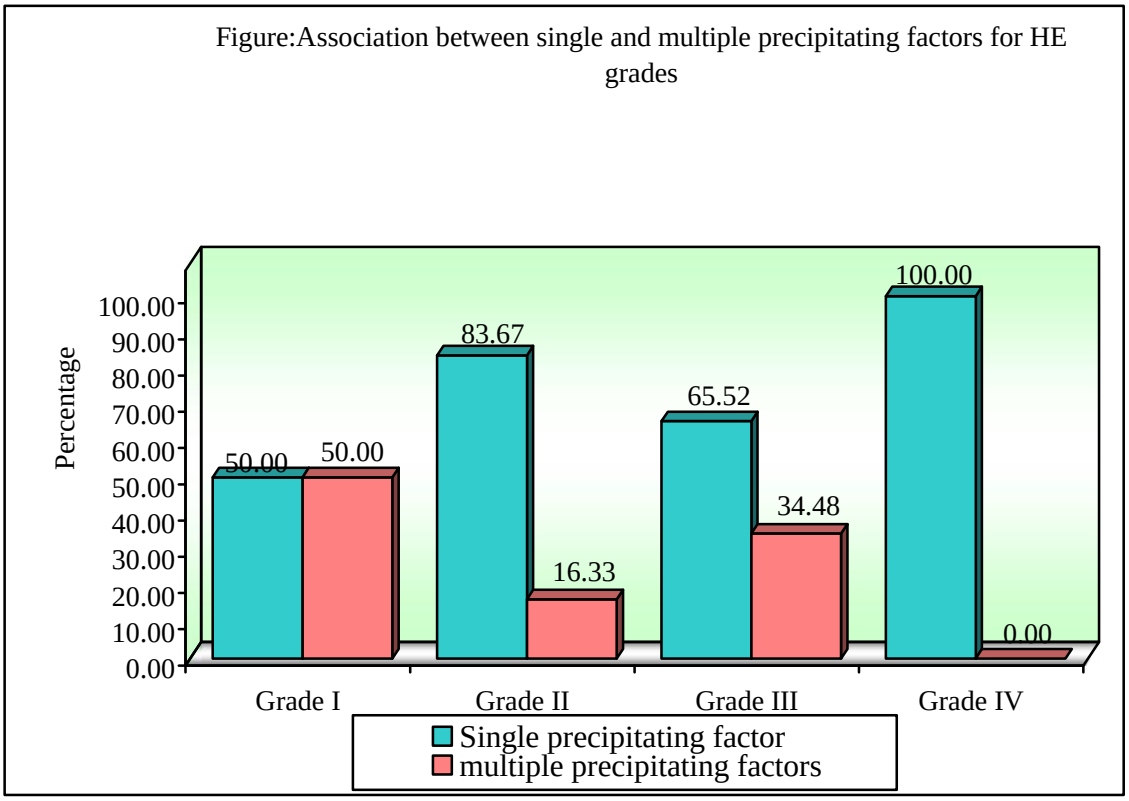


FIgure 12 Grade I HE showing equal association with single and multiple precipitating factors,

Grade II HE,43 (83.67%) were having single precipitating factor.

65.5% of patients of Grade III HE had single precipitating factor.

All Grade IV, all were showing assosciation with single precipitating factor.

There is no association between grade of HE to number of precipitating factors as P=0.1212 .

Table: 15 Association between Infection (Spontaneous bacterial peritonitis + other infections) with HE grades

HE grades	Infection + Spontaneous bacterial peritonitis				
	Absent	%	Present	%	Total
Grade I	1	50.00	1	50.00	2
Grade II	26	53.06	23	46.94	49
Grade III	19	65.52	10	34.48	29
Grade IV	3	75.00	1	25.00	4
Total	49	58.33	35	41.67	84

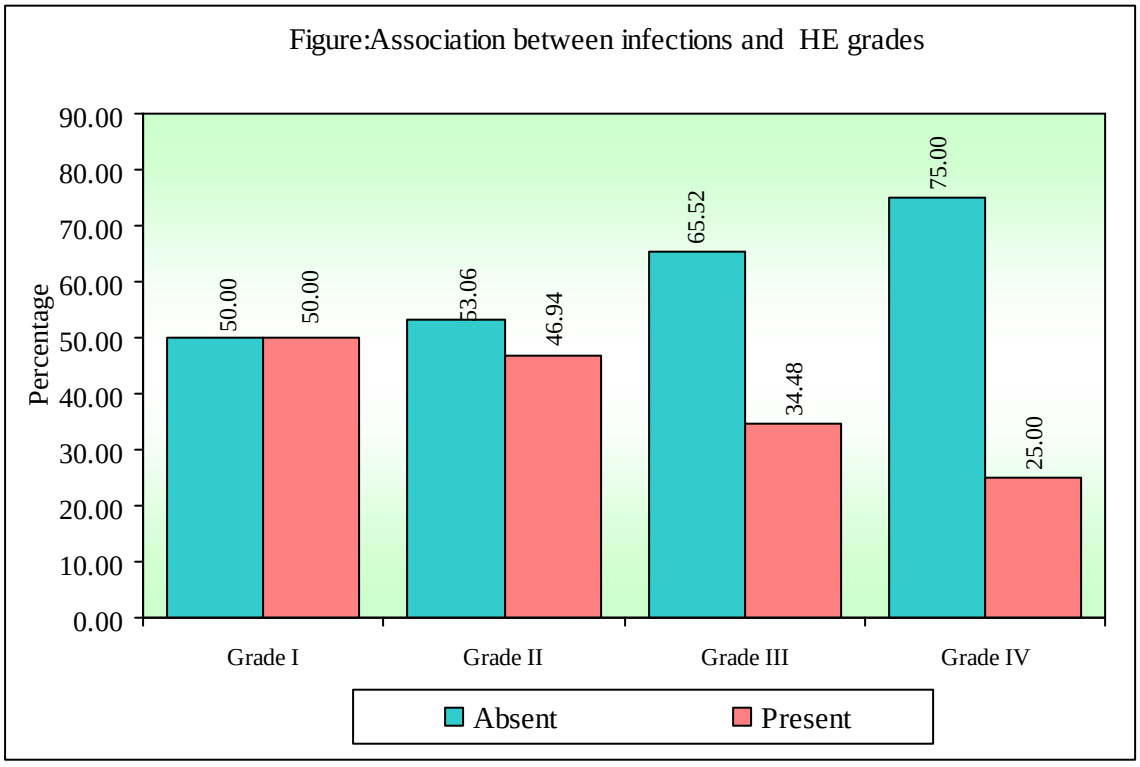


Figure 13 Among 2 patients of Grade I, one was having infection. Among 49 patients of Grade II ,23(46.94%) were having infection. Among 29 patients of Grade III,10(34.48%) were having infection. Among 4 patients of Grade IV , only 1 patient was having infection.

Table: 16 Upper GI bleeding to grade of HE

GRADE OF HE	PRESENT	ABSENT
GRADE I	0	2
GRADE II	5	44
GRADE III	19	10
GRADE IV	3	1
TOTAL	27	57

70.37%(19 out of 27) patients with upper GI bleeding had Grade III HE.

Table:17 Electrolyte imbalance to HE grade

GRADE OF HE	PRESENT	ABSENT
GRADE I	2	0
GRADE II	21	28
GRADE III	6	23
GRADE IV	0	4
TOTAL	29	55

75%(21 out of 28) patients presented with electrolyte imbalance had Grade II HE.

Table: 18 Child Pugh score with Grade of Hepatic encephelopathy

Grade of HE(WHC)	Child Pugh class B	Child Pugh class C	Total
Grade I	2	0	2
Grade II	41	8	49
Grade III	5	24	29
Grade IV	0	4	4
Total	48(57.14%)	36(42.86%)	84

Grade of HE is directly proportional to Child Pugh Class.

Table: 19 Association between Infection (Spontaneous bacterial peritonitis + other infections) with other causes of Hepatic Encephelopathy

Causes	Infection (SBP + other infections)					
	Absent	%	Present	%	Total	%
Upper GI bleeding	24	88.89	3	11.11	27	0.0001*
Hyponatraemia	13	92.86	1	7.14	14	0.0040*
Hypomagnesemia	6	85.71	1	14.29	7	0.1250
Hyperkalaemia	9	100.00	0	0.00	9	0.0070*
Hypocalcaemia	0	0.00	0	0.00	0	1.0000
Constipation	4	100.00	0	0.00	4	0.0830
Hepatorenal syndrome	7	70.00	3	30.00	10	0.4250

P<0.05

Figure: Association between total of Infection with other causes of Hepatic Encephelopathy

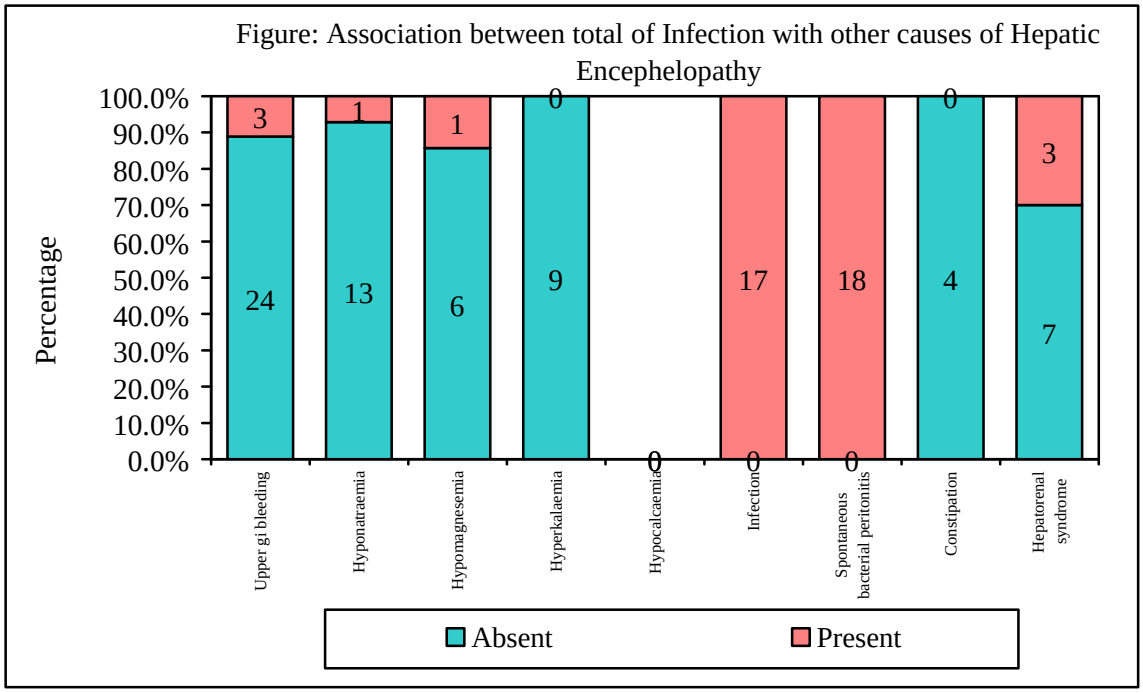


Figure 14 :Above figure shows presence of infection as a precipitating factor along with other factors causing HE.

3 patients of upper GI bleeding had infection.

1 patient of hyponatremia had infection.

3 patients of hepatorenal syndrome had infection.

DISCUSSION

This study was conducted in KLES DR.PRABHAKAR KORE HOSPITAL AND MRC, BELGAUM. A total of 84 patients of CL with HE have participated. There are maximum number of patients in age groups of 31-60 years 80.95% (68). 81 are male and 3 paients are female. According to level of education 40.48%(34) patients were illiterates.

In this study infection (SBP + other infections) 41.66%(35) is the commonest precipitating factor for HE, followed by electrolyte imbalance34.52(29), upper GI bleeding in 32.14%(27) of patients and constipation 4.76%(4). In this study serum calcium levels were also tested where corrected calcium level was taken into consideration but not even a single case of HE is associated with hypocalcaemia.

In our study infections (SBP + other infections) 41.66%(35) is the commonest precipitating factor. Among the infections spontaneous bacterial peritonitis 21.43%(18) is the commonest precipitating factor followed by other infections 20.41%(17) includes cellulitis of extremities and abdominal wall 9.52%(8) , 5.95%(5) cases are pneumonia, 2 are of acute gastroenteritis and other 2 are undiagnosed but presented with fever and raised leucocyte count. In study by Yahia Z Gad[154] only 15.61%(37 out of 237) patients had infection as a precipitating factor for HE. In a study by Bikha ram Devrajini, syed zulfiquar ali shah, Tarachand Devrajini, Dileep kumar[155] showed infection67%(58 out of 87) as a most common precipitating factor for HE. In a study by Fakhar Ali, Shameem behram khan, Anam umar[156] infection 36.6%(55 out of 96) is second most common cause for HE which is preceeded by constipation.

Electrolyte imbalance is seen in 34.52%(29) patients. In electrolyte imbalance hyponatremia16.67%(14) is the most commonest electrolyte disturbance causing HE. Out of 14 patients 12 patients are on diuretic therapy for ascitis.

Hepatorenal syndrome was seen in 11.90%(10) patients as a cause of precipitating factor for HE. Hyperkalemia was seen in 10.71%(9) patient. 9.52%(8) patients had hyperkalemia secondary to hepatorenal syndrome.

In our study hypomagnesaemia 8.33%(7 cases) as a precipitating factor for HE. These patients had showed dramatic response within few hours after correction of serum magnesium levels.

In study by Yahia Z Gad electrolyte imbalance is seen in only 2.95%(7 cases) of patients. In a study by Bikha ram Devrajini, syed zulfiquar ali shah, Tarachand Devrajini, Dileep kumar showed electrolyte imbalance in 10.34% (9 out of 87) of patients. In a study by Fakhar Ali, Shameem behram khan, Anam umar[156] electrolyte imbalance was seen in 29.33%(44cases). Our study was comparable to Fakhar ali Shameem behram khan, Anam umar.[156]

Upper GI bleeding is the third most common 32.14%(27 patients) cause for hepatic encephalopathy with most of the patients having esophageal varices than gastric varices.In a study by Bikha ram Devrajini, syed zulfiquar ali shah, Tarachand Devrajini, Dileep kumar upper GI bleeding is seen in 45%(39 out of 87) of patients. In study by Yahia Z Gad 36.7% patients showed upper GI bleeding. In a study by Fakhar Ali, Shameem behram khan, Anam umar[156] upper GI beeding was present in 34% of the patients. Our findings are comparable to most of the studies

In our study constipation is seen in 4.76%(4) of patients. In study by Yahia Z Gad[154] constipation is seen in 49%(43) of patients.

Among the participants (N=84) Grade I HE is seen in only 2.38%(2) cases, 58.33%(49) patients have grade II hepatic encephelopathy, 34.52%(29) have grade III HE, 4.76%(4) have grade IV HE. In study by Yahia Z Gad[154] 33.76%(26) patients had Grade III HE, and 53.24%(41) patients had Grade IV HE

Our observation in relation to HE grade to number of precipitating factors. Grade I HE showing equal association with single and multiple precipitating factors, Grade II HE,43 (83.67%) were having single precipitating factor. 65.5% of patients of Grade III HE had single precipitating factor. All Grade IV HE had single precipitating factor.

Our observation in relation to HE grade and infection shows that Among 2 patients of Grade I, 50%(1) had infection. Among 49 patients of Grade II ,23(46.94%) were having infection. Among 29 patients of Grade III,10(34.48%) were having infection. Among 4 patients of Grade IV , only 25%(1) patient was having infection. In study by Yahia Z Gad[154] infection is seen in 11.68%(9) patients with Grade IV HE and 5.19%(4) patients with Grade III HE.

In our study 27 patients had upper GI bleed. 19 patients (out of 27) had Grade III HE. 29 patients had electrolyte imbalance. 21 patients (out of 29) had Grtade II HE.

In our study 57.14%(48) patients had Child Pugh class B and 42.86%(36) had Child Pugh class C. Correlation of child Pugh class and HE Grade showed that

child Pugh class is directly proportional to Grades of HE. In study by Yahia Z Gad[154] a total of 37.66%(29) patients had child Pugh class B and 62.34%(48) had class C.

CONCLUSION

Infection is the commonest risk factor for hepatic encephalopathy, followed by electrolyte imbalance, upper GI bleeding, HRS, and constipation.

In our study we observed that hypomagnesemia is a precipitating factor for HE. Role of magnesium in causing HE in patients of CL is important as correction of it shows a dramatic response in patients with hypomagnesemia. So monitoring of serum magnesium level is important in apatient with HE. As sample size of present study is small larger studies are required to confirm the role of magnesium as a precipitating factor for HE in cirrhosis of liver patients.

SUMMARY

Hepatic encephelopathy(HE) is a syndrome observed in patients with cirrhosis of liver. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of brain disease[1]. The present study is aimed at studying precipitating factors for hepatic encephalopathy in cirrhosis of liver.

As early detection of precipitating factors might help in prevention of further episodes of hepatic encephalopathy thus decreasing morbidity and mortality.

This study was conducted in KLES DR.PRABHAKAR KORE HOSPITAL AND MRC, BELGAUM. A total of 84 patients have been studied which showed following results.

- There are maximum number of patients in between age group of 31-60 years 80.95% (68).
- Among 84 patients only 3 patients are female and remaining all are male patients.
- According to level of education 40.48%(34) patients were illiterates.
- Infection 41.67%(35) is the most common precipitating factor for HE. 32.14%(27) patients had upper gi bleeding. Electrolyte imbalance seen in 34.52 %(29) patients. Hepatorenal syndrome is seen in 11.90%(10) patients. Constipation is seen in 4.76%(4) patients.
- In this study ,spontaneous bacterial peritonitis is present in 21.43%(18) patients of HE . infections 20.24%(17) is cause for HE.
- GI bleed is present in 32.14%(27) of patients of HE.
- Electrolyte imbalance is seen in 34.52%(29) patients. In electrolyte imbalance hyponatremia 16.67%(14) is the most commonest electrolyte disturbance causing HE.

- Hepatorenal syndrome was seen in 11.90%(10) patients as a cause of precipitating factor for HE. Hyperkalemia was seen in 10.71%(9) patient. 9.52%(8) patients had hyperkalemia secondary to hepatorenal syndrome.
- In our study hypomagnesaemia 8.33%(7 cases) is seen as precipitating factor for HE. These patients had showed dramatic response within few hours after correction of serum magnesium levels.
- constipation is seen in 4.76%(4) of patients.
- Among the participants (N=84) Grade I HE is seen in only 2 cases, 58.33%(49 patients have grade II hepatic encephelopathy, 34.52%(29) have grade III HE, 4.76%(4) have grade IV HE.
- Grade I HE showing equal association with single and multiple precipitating factors, Grade II HE,43 (83.67%) were having single precipitating factor. 65.5% of patients of Grade III HE had single precipitating factor. All Grade IV, all were showing assosciation with single precipitating factor.
- Among 2 patients of Grade I, one was having infection. Among 49 patients of Grade II ,23(46.94%) were having infection. Among 29 patients of Grade III,10(34.48%) were having infection. Among 4 patients of Grade IV , only 1 patient was having infection. In 84 patients of HE,35(41.67%) were precipitated by infection,. in which Grade II was common.
- In our study 57.14%(48) patients had Child Pugh class B and 42.86%(36) had Child Pugh class C. As grade of HE increases so does child Pugh score and child Pugh class of the patients which shows increased mortality during next 2 years in patients presenting with higher grade of HE.

In our study we observed that hypomagnesemia is a precipitating factor for HE. Role of magnesium in causing HE in patients of CL is important as correction of it shows a dramatic response in patients with hypomagnesemia. So monitoring of serum magnesium level is important in apatient with HE.

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156. Fakhar Ali Qazi Arisar1 , Shameem Behram Khan2 , Anam Umar2 1 Department of Medicine, Section of Gastroenterology, Aga Khan University Hospital http://nepjol.info/index.php/AJMS DOI: 10.3126/ajms.v6i2.11099

INFORMED CONSENT

Title of research study: PRECIPITATING FACTORS OF HEPATIC ENCEPHELOPATHY- A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY.

Introduction and purpose:-

Hepatic Encephelopathy is a well recognised clinical complication of cirrhosis of liver and the presence and prompt identification of well defined precipitating factors is extremely important in diagnosis and treatment of this fatal condition. About 30% of patients with cirrhocis of liver die due to hepatic coma. Early diagnosis of Hepatic Encephelopathy precipitating factors can improve the outcome.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood, urine and ascetic fluid samples for the necessary investigations.

Risks and benefits:

The only risk and possible discomfort you might get is while taking blood and ascetic fluid samples for the investigations. It may cause swelling, pain, redness bruising or infection(rarely happens) at the site from where the samples are drawn.

Benefit is recognising the well defined precipitating factors of hepatic encephalopathy in cirrhosis of liver to prevent mortality.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. WInformation from this study may be published but your identity will be confidential in any publication.

Institution/sponsors/compensation:

In case of any injury related to the study, treatment will be made available at KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belgaum. There is no compensation or payment for such medical treatment by law.

Financial incentives for participants:

You will not be paid/offered any gifts/incentives for participating in the study.

Authorisation to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

Questions/contact details

In case of the queries during study you may contact following persons.

1)Dr P Krishna Prasad,

Investigator,

PG in General Medicine,

JNMC, Belgaum.

Phone no: 08105338926

2)Dr REKHA S PATIL

PROFESSOR AND HOD,

Dept of General Medicine,

JNMC, Belgaum.

phone no: 09448371125

In case of any queries regarding your rights as participant you can contact the following person

3) Dr. Ganga Pilli, Chairman,

J.N.M.C Ethical committee for human research

Phone no: 08312471350

Extn: 1527

Consent statement by patient

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this consent form, and have had all the questions answered.

Name of the participant:_____

Signature/Thumb print:_____

Name of the witness:_____

Signature/Thumb print:_____

Investigator name:_____

Signature:_____

Date: Place:

Consent statement by relative

I voluntarily agree for the participation of my _____ to take part in this study by signing below. I may withdraw my_____ at any time. I am not giving up any of my_____ legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this consent form, and have had all the questions answered.

Name of the participant:_____

Signature/Thumb print:_____

Name of the legal representative:_____

Signature/Thumb print:_____

Investigator name:_____

Signature:_____

Date: Place:

PROFORMA

CASE No:

NAME: **AGE/SEX:**

IP NO: **ADDRESS:**

OCCUPATION:

COMPLAINTS AT PRESENTATION:

PAST HISTORY:

TREATMENT HISTORY:

PHYSICAL EXAMINATION:

GENERAL CONDITION :

PALLOR: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema : Yes/No

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Systemic examination:

R.S.:

CVS:

PA:

CNS

INVESTIGATIONS:

IMAGING:

BLOOD INVESTIGATIONS:

KEY TO MASTER CHART

HEPATIC ENCEPHALOPATHY

GRADE I : 1

GRADE II : 2

GRADE III : 3

GRADE IV : 4

M : MALE

F : FEMALE

Hyponatraemia : sodium level < 135 meq/L

Hyperkalaemia : potassium > 5.5 meq/L

Hypomagnesemia : magnesium<1.8 meq/L

Hypocalcemia : corrected calcium <8.8mg/dL

PATIENT DEMOGRAPHICS								CAUSES OF HEPATIC ENCEPHELOPATHY												
CASE NUMBER	OUTPATIENT / INPATIENT NUMBER	PATIENT NAME	AGE (years)	GENDER	ADDRESS	OCCUPATION	EDUCATION	UPPER GI BLEEDING	HYPONATRAEMIA	HYPOMAGNESEMIA	HYPERKALAEMIA	HYPOCALCAEMIA	INFECTION	SPONTANEOUS BACTERIAL PERITONITIS	CONSTIPATION	HEPATORENAL SYNDROME	HEPATIC ENCEPHELOPATHY GRADE		CHILD PUGH SCORE	CHILD PUGH CLASS
1	646309	ANAND KOPP	31	M	Kudanur village, Kolhapur	MASON	5th Std	1									3		10	C
2	643170	ASHOK BADIGER	49	M	Shahapur Galli, Belagavi	Agriculturist	10th Std							1			2		9	B
3	646347	ASHOK JAMBOTAKAR	46	M	Hindalga, Belagavi	FARMAR	10th Std	2									3		11	C
4	644924	BABURAO BHAMBURE	53	M	Vengurla, Sindhudhurg	CLEARK	8th Std							2			2		8	B
5	642513	BASEPPA DHAREPPENNAVAR	55	M	Bailhongal Taluk, Belagavi	BUSINESS	BCOM			1				3			1		7	B
6	646238	DAYANAND	57	M	Gokak Taluk, Belagavi	Agriculturist	6TH STD	3						4			3		11	C
7	646702	NITIN ANKLE	43	M	Majgaon, Belagavi	DOCTOR	MBBS		1				1				2		8	B
8	644615	GOUDAPPA HOSAMANI	55	M	Chandgad Taluk, Belagavi	BUSINESS	7th Std				1					1	2		7	B
9	644861	HUSSAIN SHEIKH	52	M	Mudhol Taluk, Belagavi	Coolie	Illiterate						2				2		8	B
10	643031	KIRAN MUTAGIKER	40	M	Padaki layout, Koppal District	BUISNESS	12th Std		2								2		9	B
11	644761	KIRAN REDDY	36	M	Satteri Taluk, Belagavi	Agriculturist	BCOM						3				3		10	C
12	643027	KRISHNAJI PATIL	80	M	Gangavathi Taluk, Koppal District	BUSINESS	12th Std		3								2		9	B
13	644568	MOHAN SANZGERI	65	M	Khavatkopp, Belagavi	BUSINESS	Illiterate				2					2	2		11	C
14	642635	NINGAPPA PATIL	55	M	Bakapur, Belagavi	BUISNESS	7th Std		4								3		11	C
15	643677	NINGAPPA PATIL	55	M	Chikka Sindagi, Belagavi	BUSINESS	4th Std	4									3		12	C
16	641935	PARASHURAM BAJANTRI	28	M	Karwar, Uttarkannada District	FARMAR	12th Std								1		2		8	B
17	642808	PRAVEEN KOLKAR	29	M	Linganur, Belagavi	RETIRED	BSC		5								2		10	C
18	642856	RAMESH KOLKAR	47	M	Kittur, Belagavi	Coolie	BCOM	5									4		12	C
19	646407	RAVINDRA PUJARI	44	M	Ramdurg Taluk, Belagavi	BUSINESS	Illiterate			2					2		2		9	B
20	647026	SALEEM DHANGE	46	M	Athani Taluk, Belagavi	MASON	7th Std	6			3					3	3		11	C
21	646148	SANJAY ASTAGI	44	M	Chikkodi Taluk, Belagavi	Agriculturist	12th Std						4				2		8	B
22	650924	ABDUL KAREEM SHEIKH	49	M	Rakaskop, Belagavi	BUSINESS	10th Std		6								2		7	B
23	647980	AMARGUNDAPPA	50	M	Honawad, Belagavi	RETIRED	Illiterate	7									3		12	C
24	652534	GUNDAVVA	49	F	Belagavi dist	HOUSEWIFE	Illiterate							5			2		10	C
25	648609	BABRUVAHAN	34	M	Hukkeri Taluk, Belagavi	BUISNESS	Illiterate	8									3		11	C
26	650332	BASAVRAJ JIRIGWAD	42	M	Kudnur, Belagavi	BUISNESS	7th Std						5				4		13	C
27	651301	EKNATH KALAL	39	M	Sangameshwar Nagar, Belagavi	BUSINESS	B.A						6				2		11	C
28	652238	JUMMAPPA BABAGI	61	M	Omkar Nagar, Belagavi	BUISNESS	10th Std	9					7				3		12	C
29	647988	KRISHNAJI KALAL	40	M	Itagi, Belagavi	Labourer	Illiterate						8				2		9	B
30	650850	MAHADEVGOUDA PATIL	61	M	Chikkodi Taluk, Belagavi	Agriculturist	BSC							6			2		8	B
31	650721	MUDIYAPPA MALAKAGOUDA	64	M	Uchagaon, Belagavi	Coolie	Illiterate							7			2		7	B
32	649942	PANDURANG MALKEI	62	M	Gandigwad Village, Belagavi	Agriculturist	Illiterate							8			2		9	B
33	666470	SUBHASH DALAL	47	M	Hukkeri Taluk, Belagavi	BUISNESS	10Th Std							9			2		8	B
34	652274	PARASAPPA NAIK	60	M	Shahpuri, Belagavi	FARMAR	B.Com	10									3		11	C
35	650058	PRAKASH MAHAJANSHETTAR	34	M	Athani Taluk, Belagavi	Agriculturist	Illiterate							10			2		10	C
36	651347	PRAKASH UGARE	54	M	Sulaga Village, Belagavi	RETIRED	BSC	11									2		9	B
37	649390	PURUSHOTTAM MAKHIJE	47	M	Tadasalur Village, Belagavi	ACCOUNTANT	12th Std	12									4		12	C
38	651957	RAJASEKHAR MAMADAPUR	39	M	Uttur, Talajara, Belagavi	Agriculturist	Illiterate								3		2		9	B
39	649932	RAJASEKHAR GAVALI	35	M	Badagandi, Bilagi, Belagavi	FARMAR	Illiterate						9				3		11	C
40	651257	RAMESH KOLKAR	47	M	Tenginkeri Galli, Belagavi	Agriculturist	Illiterate	13									3		12	C
41	649108	RIYAZ NADAF	32	M	Dhonawad, Karagaon, Belagavi	BUISNESS	7th Std	14									4		12	C
42	647816	SHANTARAM KOLLI	74	M	Good Shepherd Rd, Belagavi	Agriculturist	Illiterate							11			2		8	B
43	650805	SHIVANAND MAMADAPUR	54	M	Koladur, Belagavi	BUSINESS	Illiterate	15									3		9	B
44	649881	SIDDAPPA GALBI	37	M	Ramdurg Taluk, Belagavi	Coolie	Illiterate		7								2		10	C
45	651933	SUBBARAO KULKARNI	54	M	Ambedkar Nagar, Belagavi	BUSINESS	6TH STD	16									3		9	B
46	648758	YASHWANTH DATANAL	35	M	R.C.Nagar, Belagavi	BUSINESS	B.Com						10				2		8	B

47	657919	ANANT SAWANT	40	M	Hukkeri Taluk, Belagavi	BUISNESS	Illiterate							12			2		7	B
48	652981	ANIL HALDANKAR	42	M	Madhalbhavi, Dharwad	FARMAR	10th Std		8								2		9	B
49	657248	BALAJI KAMATE	35	M	Kangrali, Khanapur, Belagavi	FARMAR	B.Sc							13			2		8	B
50	657547	BASAVARAJ MADANI	36	M	Yadur Taluk, Belagavi	Agriculturist	Illiterate							14			2		10	C
51	653588	MAHADEVGOUDA PATIL	61	M	Itagi, Belagavi	FARMAR	Illiterate		9								3		11	C
52	656691	MARUTI PUJAR	55	M	Shahapur Galli, Belagavi	BUSINESS	B.E			3							2		8	B
53	655374	PANDURANG SHANBHAG	54	M	Hindalga, Belagavi	BUSINESS	12th Std				4					4	1		7	B
54	654067	RADHABAI GURLAHOSUR	73	M	Vengurla, Sindhudhurg	BUSINESS	10th Std	17									3		9	B
55	658113	BASAVANNEVVA SALUKHE	58	F	Bailhongal Taluk, Belagavi	HOUSEWIFE	Illiterate	18			5					5	3		10	C
56	653930	SHIVANAND MAMADAPUR	54	M	Gokak Taluk, Belagavi	ACCOUNTANT	BE									6	2		8	B
57	652745	SURESH HALKARNI	43	M	Majgaon, Belagavi	FARMAR	Illiterate	19									3		11	C
58	654755	TUKARAM POTADAR	45	M	Chandgad Taluk, Belagavi	BUSINESS	7th Std							15			2		8	B
59	656093	VIJAYASINHA RAJPUT	44	M	Mudhol Taluk, Belagavi	BUISNESS	B.A							16			2		7	B
60	655571	VITTAL PATIL	47	M	Padaki layout, Koppal District	BUISNESS	Illiterate		10								2		8	B
61	664026	BASAVRAJ KOLLI	48	M	Satteri Taluk, Belagavi	FARMAR	10th Std						11				3		10	C
62	662774	BASAYYA ULAVANNAVAR	60	M	Gangavathi Taluk, Koppal District	Agriculturist	4th Std						12				3		9	B
63	654717	GANGARAM	58	M	Khavatkopp, Belagavi	BUISNESS	Illiterate	20			6					7	3		10	C
64	653588	MAHADEVAGOUDA PATIL	61	M	Bakapur, Belagavi	BUISNESS	Illiterate		11								3		11	C
65	668140	CHANNAPPA LOKAPUR	50	M	Chikka Sindagi, Belagavi	BUSINESS	Illiterate						13				3		12	C
66	664798	DATTA KURANGI	29	M	Karwar, Uttarkannada District	BUISNESS	B.Com	21									2		9	B
67	669503	DUNDAPPA BHANGI	39	M	Linganur, Belagavi	BUSINESS	Illiterate			4							2		8	B
68	664913	GANGAMMA YABARATTI	45	F	Kittur, Belagavi	Coolie	Illiterate		12								2		7	B
69	665554	HUSSAINSAB TALAVAR	37	M	Ramdurg Taluk, Belagavi	ACCOUNTANT	Illiterate	22						17			3		9	B
70	667994	ISHWAR KANABUR	34	M	Athani Taluk, Belagavi	BUSINESS	Illiterate			5							2		7	B
71	667182	MALLAPPA GADADAVAR	51	M	Chikkodi Taluk, Belagavi	FARMAR	Illiterate	23			7					8	2		8	B
72	665272	MALLIKARJUN KOUJALGI	50	M	yallapur	CLEARK	Illiterate							18			2		9	B
73	663844	NAGARAJ KALAL	33	M	guddapur	RETIRED	7th Std						14				3		10	C
74	669153	NARAYAN CHADACHAL	68	M	Sangameshwar Nagar, Belagavi	Housewife	BCOM	24									3		11	C
75	669543	RAJU KOKATANUR	45	M	Omkar Nagar, Belagavi	RETIRED	BE						15				2		8	B
76	661731	BASAVARAJ SATVAGOL	42	M	Itagi, Belagavi	BUSINESS	Illiterate			6					4		2		8	B
77	669004	SHAILENDRA KALLANDI	44	M	Mudhol Taluk	BUSINESS	B.Sc		13								2		9	B
78	667942	SHANKAR DURAGAD	45	M	Uchagaon, Belagavi	RETIRED	B.Com	25									2		10	C
79	663111	HUSSAINSAB TALAVAR	56	M	Gandigwad Village, Belagavi	FARMAR	Illiterate			7							2		9	B
80	733198	MAHADEV TAHASILDAR	57	M	Tadasalur Village, Belagavi	ACCOUNTANT	12th Std						16				3		11	C
81	663347	MAHADEVAGOUDA PATIL	61	M	Uttur, Talajara, Belagavi	Agriculturist	Illiterate		14		8					9	2		9	B
82	662793	MALLIKARJUN KAMBLE	54	M	Athani Taluk, Belagavi	Agriculturist	B.Sc	26									3		10	C
83	663648	NAGARAJ HIREMATH	30	M	Belagavi dist	BUISNESS	7th Std	27			9					10	2		9	B
84	659365	PRAKASH MAHAJANSHETTAR	34	M	Tadasalur Village, Belagavi	FARMAR	BCOM						17				2		7	B