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MAXIMIZING TREATMENT SUCCESS IN HEPATIC ENCEPHALOPATHY: A COMPREHENSIVE FRAMEWORK FOR ENHANCED OUTCOMES

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ABSTRACT

Hepatic encephalopathy (HE) is a neuropsychiatric disorder arising from portosystemic venous shunting, independent of inherent liver disease. This study aims to explore an effective management strategy for complications associated with liver cirrhosis. The literature review highlights the prevalence of HE, affecting up to 20% of decompensated cirrhosis cases and 50% of patients with transjugular intrahepatic portosystemic shunt (TIPS). The survival probability at one and three years is approximately 42% and 23%, respectively. The underlying causes of HE involve factors such as renal failure, gastrointestinal bleeding, infections, electrolyte imbalance, and medication non-compliance. HE is clinically categorized into three types, with Type C being the most common and often associated with cirrhosis. Pathophysiological mechanisms include inflammation, oxidative stress, impaired brain energy metabolism, neurotoxins, and blood-brain barrier permeability. Ammonia plays a central role, accumulating in the brain due to liver dysfunction and portosystemic shunting. Patients with cirrhosis often exhibit disturbances in intestinal flora, contributing to the pathophysiology of HE. Neurological and psychiatric manifestations vary from mild cognitive impairment to severe unconsciousness. Diagnosis relies on the West Haven criteria, assessing mental status and neuromotor function. Laboratory abnormalities include elevated bilirubin, liver enzymes, and ammonia levels. Various neuropsychiatric tests, such as the number connection test (NCT), Psychometric Hepatic Encephalopathy Score (PHES), inhibitory control test (ICT), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), aid in diagnosis. Treatment options encompass nonabsorbable disaccharides, antibiotics (e.g., rifaximin), L-ornithine laspartate (LOLA), and

zinc. Prophylactic measures, including avoiding central nervous system depressants and intubation for at-risk patients, are recommended. This study provides a comprehensive overview of HE, addressing its clinical manifestations, diagnostic modalities, and various treatment options. The proposed management strategy aims to improve patient outcomes by considering the multifactorial nature of this complex condition.

INTRODUCTION

Hepatic encephalopathy (HE) is a disorder of neuropsychiatric dysfunction brought about by portosystemic venous shunting, regardless of inherent liver infection. Patients with hepatic encephalopathy frequently present with the beginning of mental status changes going from unpretentious psychologic anomalies to significant unconsciousness. Indications of neuromotor weakness incorporate hyperreflexia, unbending nature, myoclonus, and asterixis (a coarse, myoclonic, "fluttering" muscle quake), which is estimated with the utilization of an asterixis seriousness scale(**Córdoba and Blei, 2007).** HE is separated into two essential parts: plain HE (OHE) and negligible HE (MHE) **(Ferenci et al., 2002)**. OHE can be analyzed clinically through a star grouping of signs and side effects, though MHE requires particular testing. It has been assessed that OHE is available in 30-45% of patients, with a yearly gamble of advancement in 20% of patient with cirrhosis. MHE is appeared by impedance in specific testing and is thought of as by a large portion of the clinicians to be a preclinical phase of OHE **(Poordad, 2007).** Hepatic encephalopathy (HE) is an exceptionally pervasive condition in patients with cutting edge liver illness, happening in 10% of patients at the conclusion of cirrhosis coming to up to 20% in decompensated cirrhosis **(D'Amico et al., 1986)**. Furthermore, up to half in patients with transjugular intrahepatic portosystemic shunt (TIPS) **(Vilstrup et al., 2014).** The clinical determination of unmistakable hepatic encephalopathy depends on two simultaneous kinds of side effects: disabled mental status, as characterized by the Conn score (likewise called West Sanctuary measures) (on a scale from 0 to 4, with higher scores showing more serious impairment), and impeded neuromotor function. Right now accessible treatment choices for HE incorporate nonabsorbable disaccharides (for example lactulose), anti-infection agents (for example rifaximin-α 550 mg) and l-ornithine laspartate (LOLA). Other potential treatments incorporate extended chain amino acids, probiotics, metabolic smelling salts scroungers and glutaminase inhibitors **(Hepatol, 2014).**

The present study is proposed to find out the management strategy to treat complications of liver cirrhosis.

REVIEW OF LITERATURE

Hepatic encephalopathy has a survival probability of approximately 42% at one year and 23% at three years. As people get older, the risk of developing hepatic encephalopathy rises. Hepatic encephalopathy affects men more frequently than women do(**Bustamante et al., 1999).** In the context of chronic liver disease, renal failure, gastrointestinal bleeding (such as esophageal varices), constipation, infection, medication non-compliance, excessive dietary protein intake, dehydration (such as fluid restriction, diuretics, diarrhoea, vomiting, excessive paracentesis), electrolyte imbalance, alcohol consumption, or the use of certain sedatives, analgesics, or diuretics are all potential causes of HE. A transjugular intrahepatic portosystemic shunt (TIPS) may result in hepatic encephalopathy in some instances (**Kenston et al., 2019).** According to the underlying hepatic condition, HE is clinically divided into three main categories. Acute liver failure patients develop type A (**Munoz, 2008).** Type B affects people who have large, non-cirrhotic portosystemic shunts but no underlying liver disease. Type C is connected with basic cirrhosis with portosystemic shunting. Type C is the most well-known structure. It can be one-time or ongoing **(Salerno et al., 2007).** The most common criteria for grading HE are the West Haven criteria (WHC). Four grades of clinically manifest HE are distinguished by this grading system. In grade I, patients show an absence of consideration and some unobtrusive character changes that are clear dominatingly to their family members. The most intriguing finding in grade II is time disorientation combined with, for instance, inappropriate behaviour and lethargy. Patients in grade III are stupefied but respond to stimuli. They are additionally perplexed for spot and circumstance and may show unusual way of behaving. In grade IV, patients are in unconsciousness (**Weissenborn, 2019).** With its capacity to neutralize numerous toxic chemicals absorbed from the gastrointestinal (GI) tract and others produced as byproducts of normal metabolism, the liver plays a central detoxifying role in the body. The majority of these toxins enter the liver through the portal venous system, where they are effectively absorbed by hepatocytes and eliminated through the low flow hepatic sinusoids. Increased hepatic resistance necessitates portosystemic shunts as liver fibrosis and cirrhosis progress, forcing the blood to bypass the liver. The accumulation of various toxins into the systemic circulation eventually reaches the brain and other organs as a consequence of this.

In addition to these changes in hemodynamics, cirrhosis has a significantly smaller effective hepatocyte mass, making it easy for even small amounts of toxins to overwhelm it (**Blauenfeldt et al., 2010).** A variety of distinct pathophysiological mechanisms, including inflammation, contribute to HE (**Jalan et al., 2004).** oxidative stress and also (**Bosoi et al., 2013).** included impaired brain energy metabolism, neurotoxins, and permeability of the blood-brain barrier (BBB) (**Rama et al., 2010).** Ammonia is mostly made in the digestive system when the intestinal flora breaks down proteins or the intestinal glutaminase breaks down glutamine (**Prakash et al., 2010).** In patients with advanced liver disease with a deficiency of hepatocyte mass and in the people who present portosystemic shunts, ammonia concentration increments at the fundamental level, selecting different organs, like muscle and kidney, for its clearance (**Wright et al., 2011).** Ammonia diffuses freely across cell membranes in its dissolved form (NH3) and is transported to the central nervous system as an ion (NH4+) via transporters, an increase in blood ammonia concentration can reach the brain. In the cerebrum, ammonia applies its malicious impacts through various pathways. To take out this expansion in ammonia, it is processed to glutamine in astrocytes applying poisonous impacts, which gives off an impression of being associated with the pathogenesis of HE neurological signs (**Córdoba et al., 2008).**

Patients with cirrhosis frequently have significant intestinal flora disturbances, including a significant overgrowth of potentially pathogenic Gram- negative bacteria in the small intestine, such as Enterobacteriaceae, Alcaligenaceae, and Streptococcaceae(**Garcovich et al., 2012).** The pathophysiology of HE also involves inflammation. In cirrhosis and fulminant hepatic failure, there has been a correlation between the inflammatory response and the onset of HE. Inflammatory mediators and oxidative stress may also contribute to neuroinflammation and cause dysfunction of the blood–brain barrier. Additionally, the negative effects of hyperammonaemia on the brain may be exacerbated by inflammation (**Shawcross et al., 2011).** Patients with advanced liver failure have elevated plasma levels of bile acids, end products of the metabolism of cholesterol, and these levels have been linked to neuroinflammation (**Millin et al., 2017).** A wide range of neurological and psychiatric manifestations are produced by HE. HE changes consideration, working memory, psychomotor speed, and visuospatial capacity in its most reduced articulation. As HE advances, character changes, like disregard, peevishness and disinhibition, might be accounted for by the patient's family members, and apparent awareness and engine capability adjustments.

Might happen. Additionally, excessive daytime sleepiness is frequently associated with disruptions of the sleep–wake cycle. (**Vilstrup et al., 2014).**

Progressive disorientation, inappropriate behavior, agitation, stupor, and eventually coma may be observed in more severe cases. Nonetheless, transient central neurological deficiencies or seizures have seldom been accounted for in HE (**Eleftheriadis et al., 2003).** After excluding unrelated neurologic and/or metabolic causes of encephalopathy, a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction is used to make the diagnosis of HE. Various laboratory and imaging modalities, such as computer tomography(CT), magnetic resonance imaging (MRI), electroencephalography (EEG), and others, may be required in the process of excluding other causes of encephalopathy(**Sanyal et al., 2010).** In patients with HE, laboratory abnormalities include elevated bilirubin, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), decreased serum albumin level, alkaline phosphatase, international normalized ratio (INR), and possible electrolyte disturbances caused by portal hypertension or diuretics. Patients with HE typically have elevated serum and arterial ammonia levels; however, the usefulness of these tests is debated due to the fact that these levels are significantly influenced by collection methods and can be falsely elevated if the sample was collected with the fist clenched, with a tourniquet, or without being placed on ice (**Bismuth et al., 2011).**

The number connection test, or NCT, is the test that is used the most frequently. In addition, the Psychometric Hepatic Encephalopathy Score (PHES), which can be administered at the bedside and consists of a battery of five paper-pencil tests, was created. These tests include the serial dotting test, the digit symbol test, and the NCT A and B (**Reddy et al., 2009).** The inhibitory control test (ICT), a computerized test of attention and response inhibition, is one of the additional tests used to diagnose HE. Patients with attention deficit disorder, schizophrenia, and traumatic brain injury were the initial targets of this test's development. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is another test that is frequently used to diagnose MHE (**Blauenfeldt et al., 2010).** The proper diagnosis and treatment of the underlying cause are necessary for effective HE treatment. Due to the frequency of infection as an underlying cause, antibiotics like rifaximin, neomycin/paromomycin/metronidazole, or vancomycin are frequently administered empirically. Extra treatment measures incorporate lactulose/lactitol (a non-absorbable osmotic diuretic that additionally helps convert ammonia to non- absorbable ammonium in

the gastrointestinal tract), LOLA (L-ornithine and L-aspartate preparation - expands the utilization of ammonia in the urea cycle to create urea), zinc (to address fundamental inadequacy normal in cirrhotic patients) either alone or in blend with one another or potentially antibiotics. Prophylactic intubation and monitoring in the intensive care unit are recommended for patients at risk of aspiration or respiratory compromise. Avoid taking medications that depress the central nervous system, like benzodiazepines, in patients who are also going through alcohol withdrawal **(Oey et al., 2018).**

AIMS AND OBJECTIVE

Aim: The primary aim of this analysis is to investigate hepatic encephalopathy, focusing on unraveling the optimal management strategies for achieving enhanced treatment outcomes.

Objective: To study optimal management strategies for hepatic encephalopathy.

MATERIALS AND METHODS

Study design and site: Patients of hepatic encephalopathy reporting at tertiary care hospital, Rajsamand.

Study population: Adult patients with hepatic encephalopathy who were being treated in a tertiary hospital were included in the investigation's study population.

Study material: Data was collected from old case records of medical record department.
Data was collected from patients reporting to general medicine between November 2022 to April 2023.

Study Duration: 6 Months Prospective and 2 Years Retrospective.

Inclusion Criteria

Male or female subject aged between 18 -70yrs.
Subject with diagnosis of hepatic encephalopathy (based on clinical, laboratory, endoscopic and ultra sonographic features).
Subject who has been hospitalized for hepatic encephalopathy.

Exclusion Criteria

Below 18 years
Pregnant women and lactating women.

Patients on other medication (AYUSH)

Patients having no diagnostic evidence of cirrhosis.

STUDY PROCEDURES

Study was retrospective and prospective, of patients of hepatic encephalopathy reporting at Ananta Institute of Medical Sciences and Research Centre. Data will be collected from case records of patients maintained in medical record department and also from general medicine department.

Data collection sheets were prepared which included the details of patient's, such as name, age, sex, including relevant history, examination details, diagnostic test (USG abdomen, endoscopy, CT SCAN, MRI) and laboratory investigation including level of serum SGOT, SGPT, serum total bilirubin, serum albumin, AG ratio, platelet count and PT- INR was collected and recorded.

Mentioned data was compiled and analyzed to record incidence and prevalence of liver cirrhosis during the duration mentioned. Analysis was also done to check the comorbidity occurring in such patients. It was further analyzed to find out the treatment options.

INVESTIGATIONS FOR HEPATIC ENCEPHALOPATHY

1) Ammonia Level Test

Ammonia levels test may be used to diagnose and/or monitor conditions that cause high ammonia level.

EEG

 Electroencephalogram (EEG) to look for seizures or specific patterns of electrical activity in the brain.

2) Clinical Diagnostic Scales

West Haven scale

HESA (hepatic encephalopathy scoring algorithm)

CHESS (clinical hepatic encephalopathy staging scale)

3) Laboratory Diagnosis Psychometric Tests

Paper and pencil tests:

PHES (psychometric hepatic encephalopathy score)

RBANS (repeatable battery for assessment of neurological status)

5. Computerized Psychometric Tests: ICT (inhibitory control test) Neuropsychometric test: critical flicker frequency test. CDR (cognitive drug research) test.

ETHICAL CONSIDERATIONS

Before proceeding with collecting data, the appropriate academic ethics committee's consent was needed. All participants gave their informed consent, which protected their privacy and confidentiality throughout the study.

STATISTICAL ANALYSIS

The data collected and compiled was entered in MS EXCEL, MS. WORD, DESCRIPTIVE TEST, ANOVA TEST.

RESULT

Table 5.1: Laboratory Investigations with Their Reference Range.

LABORATORY INVESTIGATIONS	NORMAL RANGE
Hb(g/dl)	11.5- 14.5 g/dl
TLC(10*3 cells/mm*3)	4.0- 11.0 (10*3 cells/mm*3)
PLA(per mlc)	150-400 10*3 cells/ul
BT(mg/dl)	0.2-1.3 mg/dl
BD/BI	0-0.3 / 0.0-1.1 mg/dl
SGPT(U/L)	13-41 U/L
SGOT(U/L)	5-35 U/L
Na(mmol/L)	136-145 mmol/L
K(mmol/L	3.5-5.1mmol/L
ALB(g/dl)	3.2-5.0 g/dl
GLO(g/dl)	2.3-3.6 g/dl
A/G	1.2-1.5
PT (secs)	12-4 secs
INR (secs)	0.85- 1.15 sec
S.Cr (mg/dl)	0.7-1.4 mg/dl

Table 5.2: Sex Distribution In Hepatic Encephalopathy.

GENDER	NUMBER OF CASES
MALE	**69**
FEMALE	**31**

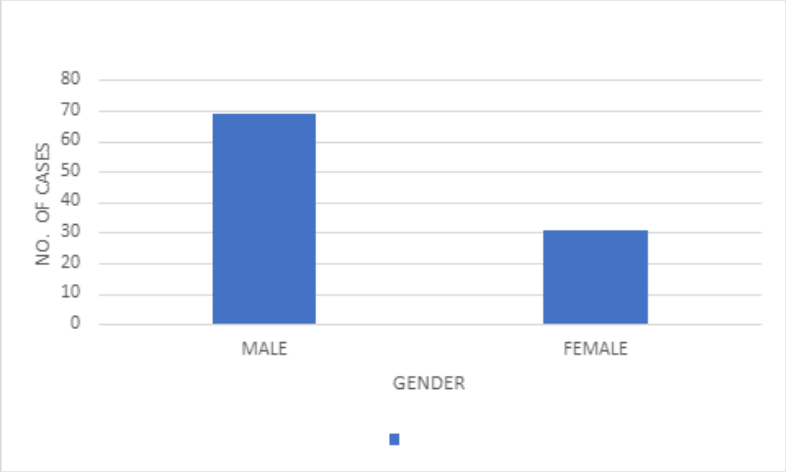

Fig. 1: Sex Distribution in Hepatic Encephalopathy.

Table 5.3: Biochemical Parameters of Patients with Liver Cirrhosis.

S. No.	Parameters	MEAN ± SD
1	Haemoglobin	9.73 ± 2.75
2	Total Leukocyte Count	9.94 ± 14.08
3	Platelet Count	255.58 ± 824.40
4	Biluribin Total	2.7 ± 4.34
5	Sgpt	40.3 ± 46.08
6	Sgot	64.38 ± 64.71
7	Sodium	134.29 ± 9.00
8	Potassium	4.53 ± 4.11
9	Albumin	2.69 ± 0.92
10	Globulin	3.45 ± 1.13
11	Pt	18.77 ± 5.76
12	Inr	1.58 ± 1.43
13	Serum Creatinine	1.59 ± 2.51

TREATMENT MODALITIES

In our study of 100 patients with liver cirrhosis, we assessed the treatment modalities used for managing the condition. The distribution of treatment options among the patients is as follows:

1. **Lactulose**: 58 patients (58%) were administered lactulose, a medication used to treat hepatic encephalopathy. Hepatic encephalopathy is a neuropsychiatric complication that occurs due to liver dysfunction, and lactulose helps reduce the levels of ammonia in the blood, alleviating the symptoms associated with this condition.
2. **Rifaximin**: 42 patients (42%) were prescribed rifaximin. Rifaximin is an antibiotic that is often used as a long-term treatment option for hepatic encephalopathy. It helps reduce the levels of ammonia-producing bacteria in the gut, thereby improving the symptoms associated with hepatic encephalopathy.

3. **Vitamin K:** 40 patients (40%) were treated with vitamin K. Vitamin K is essential for proper blood clotting, and its supplementation is often necessary in individuals with liver cirrhosis who may have impaired clotting factors.
4. **LOLA (L-ornithine L-aspartate)**: 21 patients (21%) received LOLA as part of their treatment. LOLA is a medication that helps reduce ammonia levels in the blood and is commonly used in the management of hepatic encephalopathy.
5. **Ursodeoxycholic acid**: 33 patients (33%) were treated with ursodeoxycholic acid. Ursodeoxycholic acid is a medication that aids in the management of certain liver conditions, such as primary biliary cholangitis, by improving bile flow and reducing liver inflammation.

Table 5.4: Treatment Modalities.

DRUGS	NO. OF CASES
Lactulose	58
Albumin	20
Vitamin K	40
LOLA	21
Ursodeoxycholic acid	33
Rifaximin	42

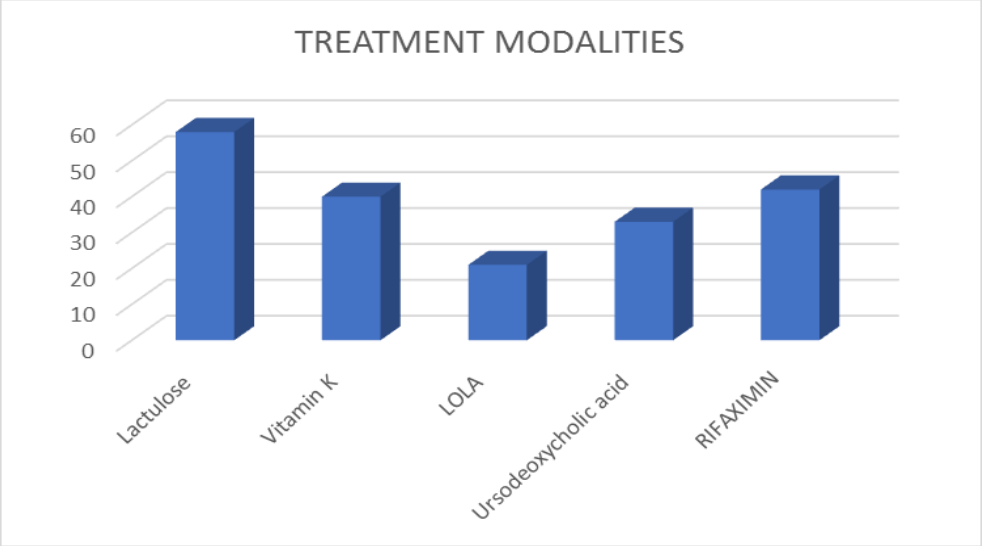

FIG. 2: Treatment Modalities.

Table 5.5: Haematological Distribution.

HB (g/dl)	NO. OF CASES
LESS THAN 12	**78**
MORE THAN 12	**22**

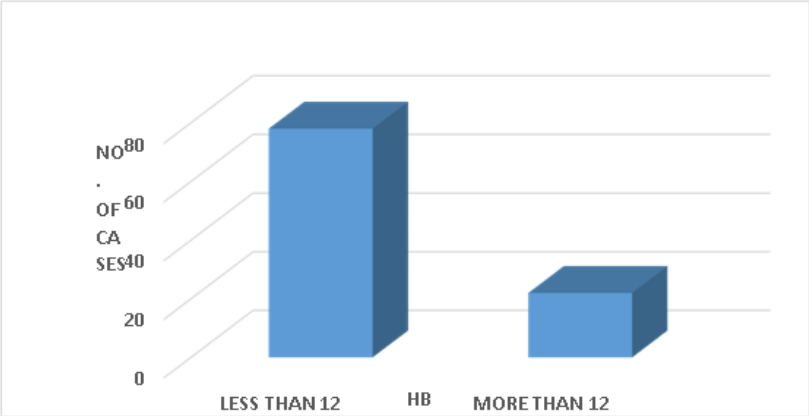

Fig. 3: Haematological Distribution.

CONCLUSION

In conclusion, liver cirrhosis is a progressive condition characterized by the development of fibrosis and nodular transformation of the liver tissue, resulting from persistent injury. It can be caused by various factors such as viral infections, toxins, genetic disorders, or autoimmune processes. The major complications associated with cirrhosis include varices, ascites, hepatic encephalopathy, portal hypertension.

Hepatic encephalopathy, a neuropsychiatric dysfunction, and its milder form, minimal hepatic encephalopathy, are caused by portosystemic venous shunting. These complications significantly impact the quality of life and prognosis of patients with cirrhosis.

Diagnosis and management of cirrhosis and its complications involve various clinical assessments, imaging techniques, and laboratory tests. Treatment strategies focus on reducing portal hypertension, managing complications, and addressing the underlying cause of cirrhosis. Pharmacological interventions, endoscopic procedures, and liver transplantation may be considered depending on the severity of the condition.

Overall, understanding the complications and management strategies in liver cirrhosis is crucial for improving patient outcomes and enhancing their quality of life. Further research is needed to explore novel therapeutic approaches and improve the prognosis of individuals with this challenging condition.

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