Introduction

Hepatic encephalopathy (HE) is a complication of liver cirrhosis that may severely affect the patients' quality of life. It has been estimated that at least 25% of patients with liver cirrhosis will experience HE during the natural history of the disease. HE is more frequent in patients with more severe liver insufficiency and in those with spontaneous or artificially created porto-systemic shunts. The neurological symptoms of HE range from sub-clinical cognitive dysfunction to overt changes in the behaviour and the state of consciousness that may reach a state of deep coma. Some patients may lack recognizable clinical symptoms of brain dysfunction but may show an abnormal performance when submitted to psychometric tests; the term "minimal HE" has been proposed to define this condition. Symptoms of HE in chronic liver disease may appear as acute reversible episodes (acute episodic HE) generally associated with a precipitating cause; neurologic symptoms may however be also recurrent, without a clear precipitating event. In a few patients, a persistent cognitive impairment may be present and negatively impact the patient's social function and everyday life (persistent HE) **(Manuela and Oliviero, 2009)**.

Patients with hepatic encephalopathy (HE) may present different neurological alterations including impaired cognitive function and altered motor activity and coordination. HE may lead to coma and death. Many of these neurological alterations are the consequence of altered neurotransmission. Hyperammonemia is a main contributor to the alterations in neurotransmission and in neurological functions in HE **(Cauli et al., 2009)**

Hepatic encephalopathy pathophysiology is still not completely understood. In this pathology, alterations in normal brain function are associated with morphological and functional impairments of astrocytes and neurons. A wide spectrum of psychoneurological symptoms has been described and the anatomical substratum is usually associated with brain edema and intracranial hypertension, as well as with changes in the function of brain cells **(Lemberg and Fernández, 2009)**.

Minimal hepatic encephalopathy (MHE) is the mildest form of spectrum of hepatic encephalopathy (HE). Patients with MHE have no recognizable clinical symptoms of HE but have mild cognitive and psychomotor deficits. The prevalence of MHE is high in patients with cirrhosis of liver and varies between 30% and 84%; it is higher in patients with poor liver function. The diagnostic criteria for MHE have not been standardized but rest on careful patient history and

physical examination, normal mental status examination, demonstration of abnormalities in cognition and/or neurophysiological function, and exclusion of concomitant neurological disorders. MHE is associated with impaired health-related quality of life, predicts the development of overt HE and is associated with poor survival. Hence, screening all patients with cirrhosis for MHE using psychometric tests, and treatment of those patients diagnosed to have MHE has been recommended **(Dhiman and Chawla, 2009).**

Therapy for MHE is targeted towards the gut, in most cases, due to the ammoniagenic potential of the gut contents, which have been hypothesized to cause HE. Lactulose and lactitol are nonabsorbable disaccharides that cause acidification of stool contents, expulsion of stool bacteria and have a laxative action **(Jasmohan and Bajaj, 2009)**.

Lactulose enema has an immediate action in ameliorating the symptoms, or preventing the occurrence of hepatic encephalopathy **(Takafumi et al., 2002)**.

Other agents, which have been shown to be effective, are mannitol and colon cleansing agents used for endoscopic procedures. In one study irrigation with 5-liter isotonic solution of mannitol by a nasogastric tube was found to be effective in preventing post-gastrointestinal bleed HE **(Rolachon et al., 1994)**.

AIM OF THE WORK

This study was conducted to evaluate the role of oral mannitol therapy in the prevention of hepatic encephalopathy in patients with liver cirrhosis and upper gastro-intestinal bleeding in comparison to rectal enema.

Hepatic Encephalopathy

Definition of hepatic encephalopathy:

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain diseases. Hepatic encephalopathy is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels **(Riggio et al., 2005)**.

Distinct syndromes are identified in acute liver failure and cirrhosis. Rapid deterioration in consciousness level and increased intracranial pressure that may result in brain herniation and death are a feature of acute liver failure whereas manifestations of hepatic encephalopathy in cirrhosis include psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration and in severe forms, coma **(Wright and Jalan, 2007)**.

A nomenclature has been proposed for categorizing hepatic encephalopathy. Type A hepatic encephalopathy describes encephalopathy associated with *A*cute liver failure. Type B hepatic encephalopathy describes

encephalopathy associated with portal-systemic *b*ypass and no intrinsic hepatocellular disease. Type C hepatic encephalopathy describes encephalopathy associated with *C*irrhosis and portal hypertension or portal-systemic shunts. Type C hepatic encephalopathy is, in turn, subcategorized as episodic, persistent, or minimal **(Ferenci et al., 2002)**.

Hepatic encephalopathy (HE) is functional in nature and potentially reversible. Signs of neurodepression characterize HE in chronic liver disease, whereas neuroexcitatory symptoms may prevail in fulminant hepatic failure **(Häussinger, 2006)**.

Classification of hepatic encephalopathy:

Table (1): Classification of Hepatic encephalopathy according to Cordoba 2004:

Hepatic encephalopathy	Liver disease	Portal-systemic shunting	Neurological manifestations	Specific features
Acute episode In cirrhosis	Cirrhosis	Variable	Confusion to coma	Usually precipitated.
In fulminant hepatic failure	Fulminant hepatic failure	Absent	Confusion to coma	Complicated by brain oedema
Chronic Relapsing	Cirrhosis	Severe	Relapsing episodes of encephalopathy	Usually without precipitating factors
Persistent	Cirrhosis	Severe	Persistent cognitive or motor abnormalities	Generally related to surgically induced shunts
Minimal hepatic encephalopathy	Cirrhosis	Variable	Asymptomatic	Abnormalities revealed by neuropsychological neurophysiological tests
In patients with porto-systemic bypass with no intrinsic liver disease	No signs of parenchymal disease	Large shunts	Relapsing episodes and persistent abnormalities	Rare disorder, secondary to congenital abnormalities or surgical shunts

(Cordoba, 2004)

The acute form is associated with fulminant liver failure and is characterized by quick progression to profound coma, seizures, and decerebrate rigidity. This variant, which is accompanied by cerebral oedema in the late stages has a high mortality rate. Deaths of patients with fulminant liver disease are due to cerebral herniation

and hypoxia, both of which are caused by increased intracranial pressure and reduced cerebral perfusion pressure ***(Souheil, 2001*)**, in patients with cirrhosis, acute encephalopathy is most commonly associated with a precipitating factor **(Blei and Cordoba, 2001).**

Recurrent HE may occur with or without a precipitating factor and is usually easily reversible. Persistent HE is rare, and is defined as the persistence of neuropsychiatric symptoms despite aggressive medical and dietary therapy. The most frequent form of HE is not always clinically apparent: a patient with subclinical HE has only mild cognitive deficits or subtle personality changes **(Blei and Cordoba, 2001)**.

Another form of hepatic encephalopathy is characterized by progressive, irreversible neurologic findings that include dementia, extra-pyramidal manifestations, cerebellar degeneration, transverse cordal myelopathy and peripheral neuropathy. It is rather rare and usually is irreversible with standard therap **(Souheil, 2001)**.

Subclinical hepatic encephalopathy: (Minimal hepatic encephalopathy)

Minimal hepatic encephalopathy is a neuro-cognitive dysfunction which occurs in an epidemic proportion of cirrhotic patients, estimated as high as 80%

of the population tested. It is characterized by a specific, complex cognitive dysfunction which is independent of sleep dysfunction or problems with overall intelligence. Although named "minimal", minimal hepatic encephalopathy (MHE) can have a far-reaching impact on quality of life, ability to function in daily life and progression to overt hepatic encephalopathy **(Bajaj, 2008)**.

Minimal hepatic encephalopathy (mHE) has been found in cirrhotic patients with normal clinical and neurological exams. Previously referred to as latent, subclinical, or Stage 0 hepatic encephalopathy, a recent consensus agreed upon the term minimal hepatic encephalopathy **(Ferenci et al., 2002)**.

It is not associated with overt encephalopathy neuropsychiatric symptoms but rather with subtle changes detected by special psychomotor tests (number connection test and the symbol Digit test) also electrophysiological tests including visual evoked potentials have been used with variable success. It is typically reversible with therapy **(Souheil, 2001)**.

Signs and Symptoms of Hepatic Encephalopathy

In patients with progressive HE, there is a gradual decrease in level of consciousness, intellectual capacity, and logical behavior along with development of specific

neurologic deficits. Two staging systems have been described. (1) Numerous studies have employed the West Haven criteria of altered mental status in patients with HE (Table 2) **(Blei and Cordoba, 2001)**. (2) Although the Glasgow Coma Scale has not been rigorously evaluated in this specific patient population, its widespread use in various other disorders of brain function makes it applicable in patients with acute or chronic liver disease (Table 3) **(Fitz, 2002)**.

Table (2): West Haven Criteria of Altered Mental Status In Hepatic Encephalopathy

Stage	Consciousness	Intellect and Behavior	Neurologic Findings
0	Normal	Normal	Normal examination; impaired psychomotor testing
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behavior	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behavior	Muscular rigidity and clonus; Hyperreflexia
4	Coma	Coma	Decerebrate posturing

Table (3): Glasgow Coma Scale of Level of Consciousness

Best Motor Response (M)	Best Verbal Response (V)	Eyes Open (E)
Obeys verbal orders 6		
Localized painful stimuli 5	Oriented and conversant 5	
Withdraws from painful stimuli 4	Disoriented and conversant 4	Spontaneously 4
Flexion in response to pain 3	Inappropriate words 3	To command 3
Extension in response to pain 2	Inappropriate sounds 2	To pain 2
No response 1	No response 1	No response 1
M+V+E = 3 to 15. Severe encephalopathy is defined as a score $\leq$ 12		

Clinical features of hepatic encephalopathy

Grading of the symptoms of hepatic encephalopathy is performed according to the so-called West Haven classification system **(Blei and Córdoba, 2001)**.

- **Grade 0** - Minimal hepatic encephalopathy (previously known as subclinical hepatic encephalopathy). Lack of detectable changes in personality or behavior. Minimal changes in memory, concentration, intellectual function, and coordination. Asterixis is absent.
- **Grade 1** - Trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia, or inversion of sleep pattern. Euphoria, depression, or irritability. Mild confusion.

Slowing of ability to perform mental tasks. Asterixis can be detected.

- **Grade 2** - Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis. Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.
- **Grade 3** - Somnolent but can be aroused, unable to perform mental tasks, disorientation about time and place, marked confusion, amnesia, occasional fits of rage, present but incomprehensible speech
- **Grade 4** - Coma with or without response to painful stimuli

Common Precipitants of Hepatic Encephalopathy

Some patients with a history of hepatic encephalopathy may have normal mental status while under treatment. Others have chronic memory impairment in spite of medical management. Both groups of patients are subject to episodes of worsened encephalopathy. Common precipitating factors are as follows:

- **Renal failure**: Renal failure leads to decreased clearance of urea, ammonia, and other nitrogenous compounds.

- **Gastrointestinal bleeding:** The presence of blood in the upper gastrointestinal tract results in increased ammonia and nitrogen absorption from the gut. Bleeding may predispose to kidney hypoperfusion and impaired renal function. Blood transfusions may result in mild hemolysis, with resulting elevated blood ammonia levels.

- **Infection:** Infection may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels.

- **Constipation:** Constipation increases intestinal production and absorption of ammonia.

- **Medications:** Drugs that act upon the central nervous system, such as opiates, benzodiazepines, anti-depressants, and antipsychotic agents, may worsen hepatic encephalopathy.

- **Diuretic therapy:** Decreased serum potassium levels and alkalosis may facilitate the conversion of NH_4^+ to NH_3.

- **Dietary protein overload:** This is an infrequent cause of hepatic encephalopathy.

(Blei and Córdoba, 2001)

Pathogenesis of hepatic encephalopathy:

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte function. Astrocytes account for about one third of cortical volume. They play a key role in the regulation of the blood-brain barrier. They are involved in maintaining electrolyte homeostasis and in providing nutrients and neurotransmitter precursors to neurons. They also play a role in the detoxification of a number of chemicals, including ammonia **(Brusilow, 2002)**.

Recent work has focused on changes in gene expression in the brain. The genes coding for a wide array of transport proteins may be upregulated or downregulated in cirrhosis and FHF. As an example, the gene coding for the peripheral-type benzodiazepine receptor is upregulated in both cirrhosis and FHF. Such alterations in gene expression may ultimately result in impaired neurotransmission **(Butterworth, 2003)**.

Ammonia hypothesis

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.

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 **(Shawcross et al., 2005)**.

Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines, and urea. Enterocytes also convert glutamine to glutamate and ammonia by the activity of glutaminase **(Chatauret and Butterworth, 2004)**.

Normally, ammonia is detoxified in the liver by conversion to urea by the Krebs-Henseleit cycle. Ammonia is also consumed in the conversion of glutamate to glutamine, a reaction that depends upon the activity of glutamine synthetase. Two factors contribute to the hyperammonemia that is seen in cirrhosis. First, there is a decreased mass of functioning hepatocytes, resulting in fewer opportunities for ammonia to be detoxified by the above processes. Secondly, portosystemic shunting may divert ammonia-containing blood away from the liver to the systemic circulation.

Normal skeletal muscle cells do not possess the enzymatic machinery of the urea cycle but do contain