



Electrolytes Disturbance and Trace Elements Changes in Different Stages of Hepatic Encephalopathy

Thesis

Submitted for partial fulfillment of Master Degree in
Internal Medicine

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2015 (A.D.)



Introduction:

Hepatic encephalopathy (HE) is a challenging clinical complication of liver dysfunction with a wide spectrum of neuropsychiatric abnormalities that range from mild disturbances in cognitive function to coma and death **(Phongsamran et al., 2010)**.

The most common form of HE is not always clinically apparent, recent evidence demonstrates individuals with minimal H.E(Grade I) have impacted driving skills and a high rate of motor vehicle accidents **(Bajaj et al., 2009)**.

The pathogenesis of HE in cirrhosis is thought to be played by circulating gut-derived toxins of the nitrogenous compounds, most notably ammonia. HE may be clinically apparent in as many as one third of cirrhotic patients **(Phongsamran et al., 2010)**.

There are different causes of hepatic encephalopathy in cirrhotic patients that include; Excessive nitrogen consumption, gastrointestinal bleeding, electrolyte or metabolic disturbance, drugs, infection and trans jugular intra-hepatic Porto-systemic shunt **(Sundaram and Shaikh., 2009)**.

Symptoms of HE may be mild like mild change in sleep pattern, thinking, and mood changes or loss of fine small hand movements. More severe symptoms include abnormal movements, agitation, seizures, slurred speech, and possibly coma (**Schuppan and Afdhal.,2008**).

The severity of HE is graded with West Haven Criteria: Grade I lack of awareness, anxiety and shortened attention span. Grade II Disorientation for time or place; inappropriate behavior. Grade III Semi-stupor but respond to verbal stimuli with gross disorientation. Grade IV Coma. (**Cash and McConville et al., 2010**)

Treatment starts by treating the cause or precipitating factor of encephalopathy & Reduction of protein in diet which helps to lower ammonia production (**Riggio and Efratiet al.,2005**)

Clinical trials have established the efficacy of lactulose enemas in the treatment of acute hepatic encephalopathy. However, patient who still have persistent chronic HE with lactulose, neomycin, metronidazole and rifaximin are second-line agents (**Al Sibae& McGuire.,2009**)

Modifications of Porto-systemic collaterals are only necessary in cases of persistent HE not respond to usual therapy (**Riggio and Efratiet al.,2005**)



Aim of the Work

Correlation between serum electrolytes level (sodium & potassium) trace elements level (zinc & magnesium) and different degrees of hepatic encephalopathy.



Chapter 1

Hepatic Encephalopathy

Introduction

The liver and the brain interact in numerous ways to ensure normal brain function. The liver plays a key role in supplying nutrients to the brain which can't produce these compounds itself. The liver removes toxic substance from blood that are harmful to the brain's nerve cells. Thus, liver dysfunction can cause disturbances of brain function and even contribute to brain damage (**Butterworth, 2003**).

Hepatic encephalopathy (HE) is a challenging clinical complication of liver dysfunction with wide spectrum of neuropsychiatric abnormalities that range from mild disturbances in cognitive function to coma and death. (**Phongsamran et al., 2010**).

HE is a common complication of advanced cirrhosis. It was estimated that one third to one half of hospitalizations for cirrhosis are related to HE. The frequency of hospitalization of HE has nearly doubled over the last decade. Patients with liver disease who develop HE have a poor prognosis (**Leevy, 2007**).

Patients with HE often have other manifestations of end-stage liver disease, such as ascites, jaundice, or gastrointestinal variceal bleeding but it can also develop as an isolated manifestation of de-compensated cirrhosis (**Carithers, 2000**).



The most common form of HE is not always clinically apparent, recent evidence demonstrates individuals who have minimal HE (Grade I) have impacted driving skills and a high rate of motor vehicle accidents **(Bajaj et al., 2009)**.

Minimal hepatic encephalopathy (MHE) which was previously known as subclinical hepatic encephalopathy has been defined as a condition in which patients with cirrhosis regardless of its etiology, demonstrates neuro-psychiatric defects, yet, having a normal mental and neurological status through global clinical examination **(Ferenci et al., 2002)**.

Severe acute or chronic liver disease and porto-systemic venous shunting are the risk factors for the development of HE. The more advanced the liver disease, the more likely the development of HE. Patients with cirrhosis who have diabetes mellitus or malnutrition or had MHE seem to develop HE more frequently with cirrhosis than others **(Munoz, 2007 and Kalaitzakis et al., 2007)**.

Pathophysiology

Understanding the pathophysiology of a disease is important in developing effective treatment goals. The broad spectrum of neuropsychiatric manifestations reflects the range of pathophysiological mechanisms, for example, impairment of neurotransmitter systems, impaired cerebral perfusion and cerebral edema, and/or atrophy that interplay with one another **(Phongsamran et al., 2010 and Poh and Chang, 2012)**.

Additionally other neurotoxic mediators or disturbed function of other neurotransmitters such as GABA and opiates may play a role in a previously stable patient with cirrhosis. The challenge remains to dissect these mechanisms for possible pharmacological intervention to improve treatment (Phongsamran et al., 2010 and Poh and Chang, 2012).

1-Ammonia:

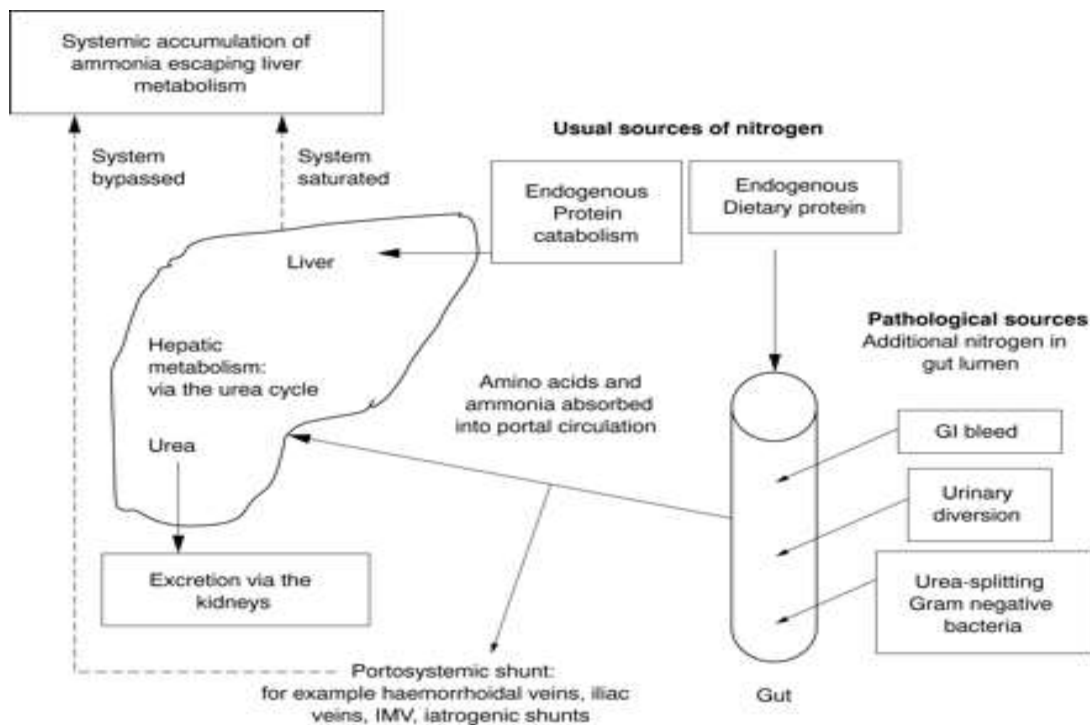


Fig A-1: Sources of nitrogen (Poh and Chang, 2012)

Hyper-ammonemia results from an increased nitrogenous load from the GIT (Fig A-1). Ammonia is produced both by bacterial degradation of amines, purines, aminoacids, and urea as well as enterocytic glutaminase activity that converts glutamine to glutamate and ammonia (Poh and Chang, 2012)



Liver failure and cirrhosis and diminished mass of functioning hepatocytes results in a decreased amount of ammonia being detoxified in the liver by conversion to urea via the Krebs cycle. In addition, portosystemic shunting also diverts a higher ammonia load to the systemic circulation by bypassing the portal system. The skeletal muscles and the kidneys compensate in ammonia metabolism with increased glutamine synthetase activity. However, astrocytes are not able to increase its glutamine synthetase activity to cope with the increased ammonia load **(Chatauret and Butterworth, 2004)**

2-Neurotoxic agents and brain oedema:

Neurotoxic agents gain entry into the brain and cause morphological changes to the astrocytes, which leads to cerebral edema, raised intracranial pressure and brain herniation. The true incidence of elevated intracranial pressure in cirrhosis and HE remains undetermined, although the presence of low grade cerebral edema in patients with HE has been reported **(Häussinger and Schliess ,2008 and Häussinger et al., 2000).**

Astrocyte swelling impairs its homeostatic ability and predisposes to neuronal dysfunction. It also induces oxidative stress by the formation of reactive oxygen species (ROS) which then goes on to cause further astrocyte swelling. In addition, astrocyte swelling also leads to a depletion of taurine which has been associated with cerebral ammonia toxicity **(Reinehr et al., 2007 and Chepkova et al., 2006).**



Taurine is the major constituent of bile and it crosses the blood brain barrier and has been implicated in a wide array of physiological phenomena including:

Inhibitory neurotransmission, membrane stabilization, feedback inhibition of neutrophil and macrophage respiratory burst and possible prevention of obesity and epileptic seizures (**Tsuboyama-Kasaoka et al., 2006**)

3-Electrolytes and trace elements:

Other factors such as hyponatraemia, inflammatory cytokines, and benzodiazepines have also shown to induce astrocyte swelling in vitro. All these may synergistically promote astrocyte swelling as a common pathogenetic endpoint. These factors may explain the presence of hepatic encephalopathy in patients with normal ammonia levels. (**Häussinger and Schliess, 2008**).

The serum sodium level was strongly associated with the severity of liver function impairment as assessed by MELD scores. Even a mild hyponatremia with a serum sodium concentration of 131-135 mmol/L was associated with severe complications as grade III or higher hepatic encephalopathy, spontaneous bacterial peritonitis and hepatic hydrothorax. (**Jong et al., 2009**)

Low levels of trace elements such as selenium, zinc and magnesium have been described to precipitate HE. Zinc deficiency is considered to precipitate hepatic encephalopathy, Magnesium deficiency occurs in alcoholic liver disease and muscle wasting. Magnesium is an independent predictor of muscle strength. This is probably related to the reduced content of sodium-potassium pumps in skeletal muscle that accompanies magnesium deficiency (**Alastair and Roger, 2008**).



The low serum zinc level is common in patient with liver cirrhosis due to decreased intake, decrease absorption, decreased bioavailability, and increased losses (because of malabsorption). There is also reduced liver protein synthesis in patients with liver cirrhosis, the metallothionein (MT) is an important zinc-binding protein (formed by liver) and is involved in zinc metabolism, homeostasis and its release in number of oxidants, the released zinc will inhibit the activity of the enzymes involved in fibrogenesis (fibrosis) in the liver, all these are yet known pathophysiological mechanisms (**Maret, 2003**)

4-Malnutrition:

Malnutrition is common in patients with end-stage liver failure and HE and adversely affects prognosis. Inadequate dietary intake, altered synthesis and absorption of nutrients, increased protein losses, hyper metabolism and inflammation are among the factors contributing to malnutrition in this patient population (**B´emeur et al., 2010**).

5-Gamma-Aminobutyric Acid (GABA), Peripheral benzodiazepine receptor (BDZ)& Neurosteroids:

The increased inhibitory function of gamma-aminobutyric acid (GABA) as well as the up regulation of the peripheral benzodiazepine receptor as a result of ammonia neurotoxicity is well known cause of astrocytes swelling and fluid accumulate in the brain (**Ahboucha and Butterworth, 2004**)



Up regulation of peripheral BDZ results in increased cholesterol uptake and synthesis of neurosteroids which have positive allosteric modulator properties on the GABA-A receptor system which could account for neural inhibition in HE. In this respect, studies found flumazenil (BDZ antagonist) leads to short-term improvement of HE in some patients with chronic liver disease and induce clinical and electroencephalographic improvement over placebo of HE in patients with cirrhosis **(Ahboucha, 2011)**.

Recently, neurosteroids such as G protein-coupled receptor (TGR5) which is a membrane-bound bile acid receptor in the gastrointestinal tract and immune cells with pleiotropic actions, expressed also in astrocytes and neurons, has also been implicated as a novel neurosteroid receptor in the brain involved in the pathogenesis of HE **(Keitel et al., 2010)**

4-Cytokines:

Cytokines are molecules secreted from immune cells as a part of immune regulatory system, and had many effects on the inflammatory process. TNF- α is the primary mediator in hepatic inflammation, and IL-1 may aggravate the lethal effects of TNF- α . Increased levels of TNF- α in patients with acute and/or chronic hepatic diseases is independent from the etiology of the liver disease. HE which developed in both acute and chronic liver disease is closely related with TNF α . Therefore inhibition of TNF- α production or blocking the effects of TNF- α or decrease of the levels of TNF- α may be an effective treatment modality in HE.

(Goral et al., 2010)



Classification

1-According to Cause:

HE is clinically classified into three major categories type A, B and C, according to the underlying hepatic condition that precipitates HE (Fig A-2): Type C is subdivided into episodic, persistent and minimal encephalopathy. (Ferenci et al., 1998).

- Type A describes hepatic encephalopathy associated with acute liver failure
- Type B is caused by portal-systemic shunting without associated intrinsic liver disease
- Type C occurs in patients with cirrhosis (Most common)

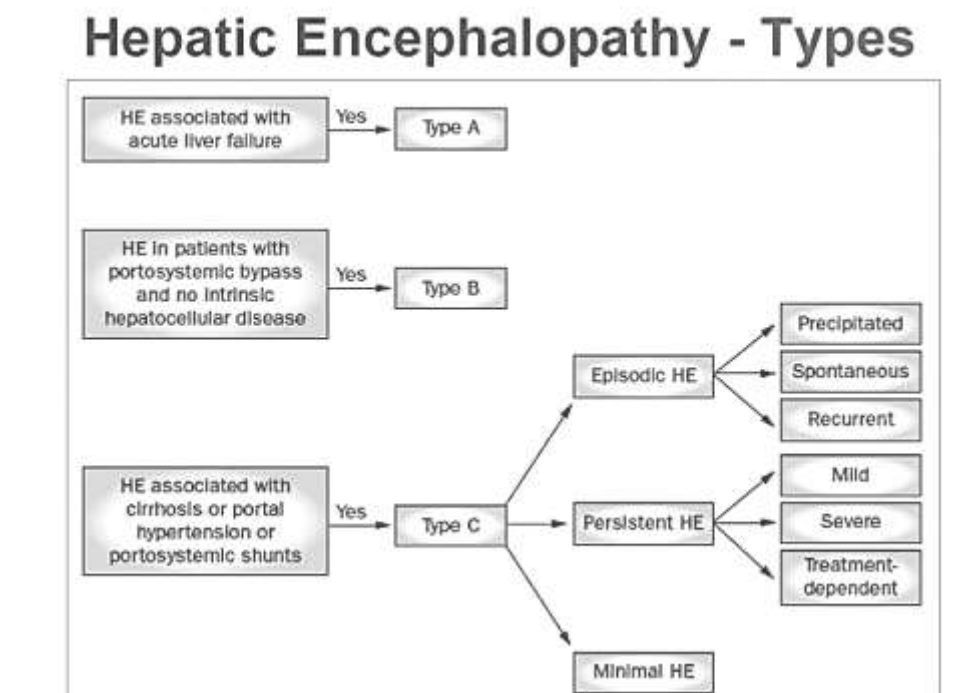


Fig A-2:Types of HE (Ferenci et al., 1998).

**2-According to clinical course and reversibility:**

HE may be presented subclinically (Minimal change HE (MHE)) and may be acute with short duration which is mostly fatal. Sometimes an episode of HE developed may not have recognizable precipitating factors (spontaneous episodic HE). If the HE lasts beyond 4 weeks or is recurrent, Persistent HE is considered (Table A-1). Both episodic and persistent HE can be adequately suppressed by therapy, but may reappear after therapy discontinuation (**Munoz, 2008**).

Table (A-1) Clinical characteristics of various forms of hepatic encephalopathy
(**Munoz, 2008**).

Form	Precipitating Factors	Clinical Course	Reversibility
Episodic	±	Short	+
Persistent	—	Continuous	+
Subclinical	—	Insidious	+

**3- According to clinical presentations: (Blei,2000).**

1. Overt HE (persistent or recurrent): This is the most common clinical presentation seen in clinical practice in patients with advanced liver cirrhosis secondary to significant porto-systemic shunting and severe hepato-cellular dysfunction.

2. Minimal hepatic encephalopathy: In patients with stable advanced liver disease may develop as cognitive abnormalities that are not clinically apparent that represent a “low grade” HE.

3. HE in acute liver failure: Cardinal feature of fulminant hepatic failure.



Diagnosis:

