Hepatic encephalopathy syndrome (HES) is a condition which occurs in patients with severely impaired detoxification function of the damaged hepatocytes of the liver because of various reasons, mostly due to cirrhosis or other liver diseases that can lead to fulminant hepatic failure. It is a neuropsychiatric syndrome characterized by disturbances in consciousness, behavior, personality, fluctuating neurologic signs and distinct EEG changes.

Background and Definition of Hepatic Encephalopathy

Hepatic encephalopathy syndrome is divided into short and long-term, which are acute and chronic types of the condition.

The former is a sequel of acute viral hepatitis A and B, toxic hepatitis as a result of severe poisoning with hazardous substances or rapid blockage of the liver blood supply, while the latter one is an after-effect of chronic hepatitis B, C and autoimmune hepatitis, long-term alcohol abuse, disordered bile outflow, certain drugs administration, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).
All diseases mentioned above are triggering factors for the development of cirrhosis that stipulates the build-up of the critical amount of toxins in the bloodstream (mainly ammonia) affecting the brain accordingly. It is crucial to exclude all possible brain diseases and CNS disorders for the diagnosis of HES, hence liver tests have to be taken into account in the first order.

Epidemiology of Hepatic Encephalopathy

The statistics for HES is quite gloomy; it is found in 70% (the overt type is detected in almost half of the patients) of cirrhosis sufferers. Moreover, the condition tends to aggravate with time, and from 25% to over 50% of those who have had portosystemic shunt surgery undergo HES.

The survival rate among patients with HES is 42% at 1 year and only 23% at 3 years; HES is always an obvious reason for frequent hospitalization. After ascites, HES is the second common reason for hospitalization in the US. The economic cost for the health providing system of the country is overwhelming, reaching the figure of $7 billion annually. Thus, HES has become a burning issue for the caregivers and the patients.

Pathogenesis of Hepatic Encephalopathy

These external and internal factors have led to the postulation of various theories that explain the pathogenesis of hepatic encephalopathy. These include:

1. Hyper ammonemia theory.
2. GABA hypothesis.
3. False neurotransmitters theory.

Hyper ammonemia theory
Certain substances like ammonia and manganese build up in the bloodstream due to a failure of elimination in the failing liver are the neurotoxins causing morphological changes in the astrocytes. This type of cells may turn into Alzheimer type 2 astrocytes in cirrhosis (swollen ones), while such transformation in Alzheimer type 2 astrocytes does not occur in ALF.

However, the cells are still swollen and often become the reason for the brain edema, increased cranial pressure, and brain herniation subsequently.

It is alleged that a majority of the patients with cirrhosis have cerebral edema and elevated intracranial pressure (ICP) confirmed on a CT scan. This condition requires particular intensive management, including the administration of intravenous mannitol, a phenobarbital-induced coma, and hyperventilation.

Elevated ammonia levels have been demonstrated in cirrhosis patients and lower levels have been recorded in patients recovering from the disease thus supporting this theory.

### GABA hypothesis

Changes in gene expression may play a pivotal role in the deterioration of neurotransmission. Thus, there are up- and down-regulation of numerous transport proteins in cirrhosis and ALF (up-regulation of the gene coding for the peripheral-type benzodiazepine receptor in both cases). This change in gene expression leads to increased GABAergic tone in patients with cirrhosis due to reduced hepatic metabolism. The receptors act in synergy with barbiturate and benzodiazepine receptors.

This theory is supported by the fact that administration of flumazenil has been shown to increase the level of consciousness in some patients suffering from hepatic encephalopathy.

### False neurotransmitter theory

This theory postulates that hepatic encephalopathy is a deadly after-effect of the last stage of liver failure that allows toxins to bypass the liver. The liver failure is associated with increased permeability of the blood-brain barrier that causes
easy penetration and accumulation of neurotoxins in the brain. These toxins include; fatty acids, mercaptans, tyramine, octopamine, and so forth.

Clinical Features of Hepatic Encephalopathy

There are two sorts of hepatic encephalopathy:

1. Covert hepatic encephalopathy (CHE)
2. Overt hepatic encephalopathy (OHE)

The former one has a very poor prognosis for the sufferers.

The West Haven classification is used for the assessment of the symptoms of hepatic encephalopathy, which includes:

**Grade 0** - minimal hepatic encephalopathy (CHE) associated with minor changes in personality, behavior, memory, coordination, concentration, intellect; absence of asterixis

**Grade 1** (difficult to diagnose) - slightly impaired awareness, short-term attention, worsened addition or subtraction, sleepiness or poor sleep, disturbed sleep, euphoria turning into the depression and vice versa, mood swings, the patients are somewhat confused, deceleration of mental activities

**Grade 2** - lethargy or apathy, aggravating disorientation, inappropriate behavior, muffled speech, avert asterixis, somnolence turning into lethargy, impairment of performance of mental tasks, obvious changes of personality, time disorientation

**Grade 3** - somnolent but may be awakened, completely unable to conduct intellectual tasks, place and time disorientation, significant confusion, loss of memory (amnesia), increased irritability (fits of rage), incomprehensible speech

**Grade 4** - coma, weak or no response to any painful stimuli

The differentiation between CHE and OHE has recently been changed, hence, the patients are considered to be “covert” being in grade 0-1, while those ones in grade 2 through 4 are “overt”.

Workup of Hepatic Encephalopathy

The hallmark of the growing probability of hepatic encephalopathy is the elevated ammonia level in the bloodstream, together with impaired mental function. It is important to mention that only arterial or venous bloods have to be examined, the analysis of the specimens from an extremity may pervert the pattern of the ammonia concentration in the bloodstream.

EEG reflects high-amplitude low-frequency waves and triphasic ones, though seizures have to be excluded here in the first order. This method is quite informative in differential diagnosis of cirrhosis and mental disorders.

CT and MRI of the brain are useful in differential diagnostics of certain brain damages and cirrhosis.

Differential Diagnostics of Hepatic Encephalopathy
Intracranial lesion (subdural hematoma, bleeding, ischemic stroke, benign and malignant tumors, abscess)
- Infectious processes in the brain tissue and its covers (meningitis, encephalitis, abscess)
- Metabolic encephalopathy
- Alcohol encephalopathy (Wernicke encephalopathy)
- Organic brain syndrome
- Epilepsy (post seizure encephalopathy)

Management of Hepatic Encephalopathy

The methods of treatment and observation for the patients with hepatic encephalopathy depend on the flow of the disease and may vary significantly regarding the grade of the encephalopathy.

**In all patients, initial stabilization must be done:**

- Maintain a patent airway and in the case of grade 3-4 encephalopathy, provide endotracheal intubation, or place the patient in the intensive care unit.
- Correction of hypovolemia and fluid resuscitation should be done.
- Administer oxygen.

**Exclusion of non-hepatic reason of encephalopathy is next which may include:**

- Regular check-ups of the ammonia level in the bloodstream in the patients with cirrhosis and aggravated mental functions
- Correction of metabolic alterations, constipation, infections, and bleedings
- Refrain prescription of drugs causing depression of CNS (benzodiazepines)

Treatment to decrease intestinal production of ammonia or increase loss of ammonia from the gastrointestinal tract is thought to be the specific method of treatment for the disease.
**Treatment to decrease intestinal ammonia production**

**Diet**

Nowadays, low-protein diets are efficient in the treatment of patients with cirrhosis and hepatic encephalopathy as the measure of prevention of the latter one. However, this method may lead to malnutrition of this category of patients, which overwhelms the positive effects of this diet.

**Cathartics**

Lactulose decreases the production of ammonia (NH₃⁺) in the intestine by the transformation of **lactulose to lactic and acetic acid** with further acidification of the gut lumen. Subsequently, ammonia turns into ammonium (NH₄⁺).

The membrane is less impermeable for NH₄⁺ and it gets trapped in the colonic lumen leading to the lowering of the level of ammonia in the plasma. Lactulose acts as a cathartic declining the load of colonic bacteria. The acidification of the gut inhibits ammonia-denitrifying coliform bacteria, thus the amount of non-ammoniagenic **lactobacilli** grows up respectively.

**Antibiotics**

In order to decrease the concentration of ammoniagenic bacteria in the colon, **neomycin**, **metronidazole**, **oral vancomycin**, and **quinolones**, as well as **paromomycin**, are efficiently administered here. Neomycin is a second-line antibiotic as it possesses ototoxic and nephrotoxic properties during long-term treatment (systematic consumption).

**Rifaximin (rifampin)** is as effective as neomycin and paromomycin in the improvement of hepatic encephalopathy at the dose of **400 mg 3 times per day** owing to the effects on the gut microflora metabolism without changing the number of the bacteria.

**Treatment to increase ammonia clearance**

**L-ornithine L-aspartate (LOLA)** increases glutamate levels.

LOLA (Hepa-Merz) has the two formulations oral and intravenous, widely spread in Europe but not in the US. There is a loss of ammonia stipulated by the stimulation of the **urea cycle by L-ornithine**.

**Zinc**

This element deficiency is characteristic in cirrhosis patients. **Zinc sulfate and acetate** (600mg orally daily) improves the situation with hyperammonemia leading to the loss of ammonia that is toxic to the brain tissue.

**L-carnitine**

The way it improves the hepatic encephalopathy course is unclear, but it does have an effect on the brain ammonia uptake and it lowers the blood ammonia level.

**Treatment to improve sleep disturbance**

This is one of the most common disorders associated with cirrhosis, thus, **H₁ blocker hydroxyzine (25 mg)** before going to bed improves the sleeping pattern in the patients with insomnia. However, this medicine has to be carefully administered as in some
patients the general condition may deteriorate on the background of this drug treatment.

References

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Hepatic Encephalopathy via webmd.com

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