Hepatic Encephalopathy: Definition, Pathogenesis, and Clinical Features

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

Hepatic encephalopathy syndrome (HES) is divided into short and long term; that is, acute and chronic types.

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. The latter is an after-effect of chronic hepatitis B, C, and autoimmune hepatitis, long-term alcohol abuse, disordered bile outflow, certain drugs, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

All the diseases mentioned above are triggering factors for cirrhosis, which refers to the build-up of critical amounts of toxins in the bloodstream (mainly ammonia), affecting the
brain accordingly. It is crucial to exclude all possible brain diseases and CNS disorders to diagnose HES; hence, liver tests are essential.

Epidemiology

HES occurs in 70% of patients with cirrhosis (the overt type is detected in almost half of the patients). Moreover, the condition tends to become aggravated with time. Between 25% and 50% of patients who had portosystemic shunt surgery undergo HES.

The survival rate among patients with HES is 42% at 1 year and only 23% at 3 years. After ascites, HES is the second most common reason for hospitalization in the US. The economic cost for the nation’s healthcare system is about $7 billion annually.

Pathogenesis

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

1. Hyperammonemia theory
2. GABA hypothesis
3. False neurotransmitters theory

Hyperammonemia
Certain substances, like ammonia and manganese, build up in the bloodstream because the failing liver cannot eliminate them; the neurotoxins cause morphological changes in astrocytes. These types of cells may turn into Alzheimer type 2 astrocytes in cirrhosis (swollen ones), while such a transformation in Alzheimer type 2 astrocytes does not occur in acute liver failure (ALF).

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

Most patients with cirrhosis reportedly 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.

**Gamma-aminobutyric acid (GABA)**

Changes in gene expression may play a pivotal role in neurotransmission deterioration. 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 the administration of flumazenil has been shown to increase the level of consciousness in some patients with HES.

**False Neurotransmitters**

This theory postulates that HES is a deadly after-effect of the last stage of liver failure and allows toxins to bypass the liver. 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.
acids, mercaptans, tyramine, and octopamine.

Clinical Features

There are two sorts of hepatic encephalopathy:

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

The former has a very poor prognosis.

The West Haven classification is used to assess the symptoms of hepatic encephalopathy, which includes:

Grade 0 – minimal hepatic encephalopathy (CHE) associated with minor personality changes, behavior, memory, coordination, concentration, and intellect, without asterixis

Grade 1 (difficult to diagnose) – slightly impaired awareness and short-term attention, worsened addition or subtraction, sleepiness or poor sleep, disturbed sleep, mood swings, confusion, deceleration of mental activities

Grade 2 – lethargy or apathy, aggravating disorientation, inappropriate behavior, muffled speech, avert asterixis, somnolence turning into lethargy, impaired performance of mental tasks, obvious personality changes, 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 was recently changed. Patients are now considered ‘covert’ in grade 0-1, while those ones in grades 2 through 4 are ‘overt’.

Work-up

The hallmark of the growing probability of hepatic encephalopathy is the elevated ammonia level in the bloodstream, together with impaired mental function. Only arterial or venous blood must be examined. An analysis of specimens from an extremity may pervert the ammonia concentration pattern in the bloodstream.

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

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

Differential Diagnostics
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

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
- Correct 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 patients with cirrhosis and aggravated mental functions
- Correction of metabolic alterations, constipation, infections, and bleeding
- 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 for treating patients with cirrhosis and hepatic encephalopathy as the measure of preventing the latter. However, this method may lead to malnutrition in this category of patients, which overwhelms this diet’s positive effects.

Cathartics

Lactulose decreases the production of ammonia (NH3+) in the intestine by transforming 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, reducing the level of ammonia in the plasma. Lactulose acts as a cathartic, declining the colonic bacteria load. The acidification of the gut inhibits ammoniagenic coliform bacteria, so the amount of non-ammoniagenic lactobacilli increases.

Antibiotics

To decrease the ammoniagenic bacteria concentration in the colon, neomycin, metronidazole, oral vancomycin, and quinolones, as well as paromomycin, are effective. Neomycin is a second-line antibiotic because it possesses ototoxic and nephrotoxic properties during long-term treatment (systematic consumption).

Rifaximin (rifampin) is as effective as neomycin and paromomycin for improving HES at the dose of 400 mg 3 times per day because of the effects on 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 two formulations, oral and intravenous. It is used widely in Europe but not in the US. The drug promotes ammonia loss by stimulating the urea cycle by L-ornithine.

Zinc

Zinc deficiency is common among cirrhosis patients. Zinc sulfate and acetate (600mg orally daily) improve 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 affect the brain ammonia uptake and lowers the blood ammonia level.

Treatment to Improve Sleep Disturbances

This is one of the most common disorders associated with cirrhosis; thus, H1 blocker hydroxyzine (25 mg) at bedtime improves sleeping patterns in patients with insomnia. However, this medicine has to be administered carefully because some patients’ general condition may deteriorate with this drug treatment.
References

Hepatic Encephalopathy via medscape.com
Hepatic Encephalopathy via webmd.com

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