Hepatic Encephalopathy
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ABSTRACT

Chronic liver disease and cirrhosis affect hundreds of millions of patients all over the world. The majority of patients with cirrhosis will eventually develop complications related to portal hypertension. One of these recurrent and difficult to treat complications is hepatic encephalopathy. Studies have indicated that overt hepatic encephalopathy affects 30 to 45% of patients with cirrhosis and a higher percentage may be affected by minimal degree of encephalopathy. All of these factors add to the impact of hepatic encephalopathy on the healthcare system and presents a major challenge to the gastroenterologist, hospitalist and primary care physician.

Key Words: Chronic liver disease, cirrhosis, hepatic encephalopathy, portal hypertension, porto-systemic encephalopathy

PATHOGENESIS

The liver has a central detoxifying role in the body with its capability of neutralizing many toxic chemicals absorbed from the gastrointestinal (GI) tract and others produced as byproducts of normal metabolism. Most of these toxins reach the liver through the portal venous system and going through the low flow hepatic sinusoids these substances are effectively captured and detoxified by hepatocytes. With the progression of liver fibrosis and development of cirrhosis the increased hepatic resistance forces the blood to bypass the liver by flowing through portosystemic shunts. This results in pooling of various toxins into the systemic circulation and eventually reaching the brain and other organs. In addition to these hemodynamic changes, the effective hepatocyte mass is significantly reduced in cirrhosis, thus it can be easily overwhelmed by relatively small amounts of toxins.

Normal brain function requires anatomical brain integrity, sufficient energy production, and efficient synaptic neurotransmission, all of which are impaired in HE. Although the mechanism of this impairment is not very clear, several factors and pathways interact together resulting in the central nervous system (CNS) dysfunction which manifests clinically as varying degrees of HE.

NEUROTOXINS

The role of ammonia in the pathogenesis of HE was proposed initially in 1890s by Nencki et al. who described the "meat
intoxication syndrome.” In their study, Nencki et al. fed dogs with large amounts of meat after creating surgical portosystemic shunts. This resulted in the development of aggressiveness, irritability, and convulsions in association with significantly elevated arterial ammonia levels. Further studies have shown that arterial levels of ammonia are elevated in patients with HE and the highest levels are noted in patients who were comatose.

The major amount of ammonia is produced in the colon by intestinal bacteria as byproduct of catabolism of ingested protein and secreted urea and enterocytes from glutamine which is their main source of energy. Another questionable source of ammonia may be urea digested by Helicobacter Pylori in the stomach, although the role of H. pylori in precipitating HE is unclear. The intact liver clears almost all of the portal venous ammonia, converting it into urea and glutamine thereby preventing its entry into the systemic circulation. In the case of cirrhosis intestinal ammonia is shunted away from the liver and eventually it gets carried to the arterial circulation and the brain where it diffuses into CNS. Impaired renal function and alkalosis due to chronic use of diuretics and intravascular volume depletion can significantly affect kidney excretion of ammonia. Muscle wasting, a common occurrence in cirrhotic patients, may also contribute to the increased levels of arterial ammonia since muscle is an important site for extrahepatic ammonia removal.

The uptake of ammonia by the brain has been proven by Bessman et al. who demonstrated that venous ammonia levels are lower than arterial levels. This absorbed ammonia is normally used by astrocytes to resynthesize gamma-aminobutyric acid (GABA) and glutamate. Further studies using positron emission tomography showed an increased ammonia uptake by the brain in patients with HE. The exact mechanisms by which ammonia causes brain dysfunction are yet to be elucidated. Nonetheless, there is evidence that ammonia is toxic to both neurons and astrocytes, the glial cells of the CNS. Astrocytes surround blood vessels and are involved in maintenance and nutrition of neurons. Neurons are more vulnerable to the effect of ammonia than astrocytes, which absorb ammonia and convert it to glutamine in order to minimize its toxic effect on neurons. This protective role of astrocytes against the toxicity of ammonia to neurons has been shown in cell culture studies.

In acute liver failure, ammonia leads to astrocyte swelling with resultant brain edema. Chronic exposure to ammonia leads to structural changes in astrocytes including large swollen nucleus, prominent nucleolus, and margination of chromatin pattern. These damaged astrocytes structurally resemble Alzheimer type II astrocytes. These changes seem to be caused by conversion of large amounts of ammonia into glutamine which interferes with mitochondrial function, leads to production of free radicals and potentially to oxidative damage of mitochondrial constituents. Further studies have shown that hyperammonemia leads to increased brain glutamine levels followed by increased brain water and deterioration in neuropsychological function. These toxic effects of ammonia interfere with both the inhibitory and excitatory neurotransmissions in the CNS with resultant inhibitory effect. In addition to that, the structural and functional changes in CNS lead to impairment of brain energy metabolism, alteration in expression of several genes coding for important functional proteins, and dysfunctional cerebral blood flow.

Several studies have suggested that hyperammonemia may increase the cerebral uptake of neutral amino acids by enhancing the activity of the L-amino acid transporter at the blood-brain barrier. The mechanisms leading to this
change have been linked to excessive conversion of ammonia into glutamine. Subsequently, large amounts of tyrosine, phenylalanine, and tryptophan shift into the CNS thereby affecting the synthesis of many neurotransmitters such as dopamine, norepinephrine, and serotonin.\[16,20\]

The absence of a strong and predicted correlation between ammonia levels and the severity of HE has led to the search for other factors contributing to the pathogenesis of HE. The multifactorial theory was first suggested in 1974 by Zieve et al. who described the possible synergistic effect of several neurotoxins including ammonia.\[21,22\]

Many toxic chemicals generated by enteric flora have been shown to potentiate the neurotoxic effect of ammonia. This includes oxindole, phenols, mercaptans, and short-chain fatty acids (C4 to C8). Oxindole is a tryptophan metabolite formed by gut bacteria from indole. This substance has been shown to cause sedation, muscle weakness, hypotension, and coma.\[23\] The cerebral concentration of oxindole has been shown to increase by 200 folds in rats with acute liver failure. Administering oral neomycin to these rats results in significant reduction in CNS concentrations of oxindole. Indole levels have been shown to be significantly higher in patients with overt HE and in patients with cirrhosis compared with controls.\[24\] In another report, indole level increased after placement of transjugular intrahepatic porto-systemic shunt (TIPS) and resulted in deterioration of psychometric performance.\[23\]

**SYSTEMIC INFECTION AND INFLAMMATION**

In addition to its metabolic and detoxifying function, the liver plays a major role as an immune organ where it is the first line of defense against infectious agents translocating from the GI tract. The sluggish blood flow through the liver parenchyma allows sufficient time for the immune cells to capture most of the microbes in the portal venous system. These hemodynamic mechanisms are altered in cirrhosis and the portosystemic shunts allow microbes to escape into the systemic blood circulation thereby resulting in a chronic state of endotoxemia and inflammation. The blood levels of endotoxins have been shown to be elevated in patients with portal hypertension. These levels are even further increased after placement of TIPS.\[12,25\] Furthermore, the elevated level of ammonia has been shown to have a deleterious effect on neutrophils leading to their swelling, impaired phagocytosis, and increased oxidative burst. The resulting immunosuppressed state explains the high rates of infection in the cirrhotic population accounting for around half of their hospital admissions.\[16,26\]

Studies have shown higher levels of serum inflammatory markers in patients with HE in comparison to those without HE regardless of the underlying severity of liver disease and ammonia level. These cytokines include tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1 β), IL-6, and IL-18.\[27\] These mediators potentiate the effect of ammonia on CNS resulting in higher levels of glutamine, decrease in brain myoinositol, and significant increase in brain water.\[25-31\] The effect of pro-inflammatory mediators on the brain is at least partially transmitted through cyclo-oxygenase (COX) pathway within endothelial cells. Blocking this pathway with the use of non-steroidal anti-inflammatory drugs (NSAID) such as indomethacin has been shown to improve intracranial hypertension and lower brain edema in patients with acute liver failure.\[32\]

Additional mechanisms involved in the pathogenesis of HE include interruption of the blood-brain barrier and abnormalities in the gamma aminobutyric acid (GABA) and benzodiazepine pathways. The liver is the major site of catabolism of GABA and studies have demonstrated elevated GABA levels in cirrhotics. Furthermore, this molecule is capable of diffusing into the brain through the disrupted blood brain barrier. In addition, increased levels of endogenous benzodiazepine-like substance has been detected in the blood, cerebrospinal fluid, and brain tissue of cirrhotics with HE.\[2,32\] Further, studies have indicated a role of neurosteroids in the pathogenesis of HE. These progesterone metabolites are endogenous neuroactive compounds that modulate the GABA-A receptor complex and induce sedation. Other studies describe alterations in serotonin metabolism and activity, decreased histamine H1 receptor activity, and altered melatonin secretion cycle in patients with HE.\[33-35\]

The exact mechanisms of HE are still unclear despite various theories trying to explain this complicated syndrome. The multifactorial theory seems to be very reasonable with increasing data to support it. Ammonia continues to play a major role in the pathogenesis of HE and it seem to act synergistically with multiple other factors including systemic inflammatory cytokines.\[36\]

**CLINICAL MANIFESTATIONS**

With advanced liver dysfunction, various systems and organs are affected and their functions are impaired including the CNS impairment that manifests as HE. In early stages of HE this impairment is minimal and may continue to be subclinical for a prolonged time. Several factors are known to disrupt the fine balance of liver function in cirrhosis thereby precipitating or worsening pre-existing HE [Table 1].\[13\]

The clinical features and presentation of HE vary based on its severity. While patients with subclinical or minimal HE (MHE) have disturbances detected only on neuropsychiatric and psychomotor testing, patients with...
overt HE may present with coma. Disturbance in the diurnal sleep pattern is a common early manifestation of HE and is related to altered melatonin secretion. More advanced neurologic features of HE include bradykinesia, asterixis (flapping motions of outstretched, dorsiflexed hands), hyperreflexia, and transient decerebrate posturing. Rarely, HE may be associated with development of transient focal neurologic deficits, the most common of which is hemiplegia. Although asterixis is commonly seen in patients with HE it is not specific to this disease and it can also be observed in patients with other forms of metabolic encephalopathies such as in uremia, respiratory failure, and barbiturate toxicity [Table 2].

Hepatic encephalopathy has been classified into four grades based on the West Haven classification [Table 3]. This grading system is based on the degree of CNS impairment reflected by neurologic, psychiatric and physical findings. More complicated grading systems are available yet they are less frequently used in clinical practice.

In contrast to overt HE, patients with minimal HE may have normal abilities in the areas of memory, language, construction, and pure motor skills. However, they demonstrate impaired complex and sustained attention that can affect their ability to drive as shown in several studies.

Patients with HE have physical and laboratory stigmata indicative of hepatic dysfunction. These findings may include muscle wasting, jaundice, ascites, peripheral edema, spider telangiectasias, palmar erythema, and fetor hepaticus.

**DIAGNOSIS**

The diagnosis of HE is based on the presence of a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of unrelated neurologic and/or metabolic causes of encephalopathy. Table 2 lists a number of disorders to be considered in differential diagnosis of HE. The process of exclusion of other causes of encephalopathy may necessitate obtaining various laboratory and imaging modalities including computer tomography (CT), magnetic resonance imaging (MRI), electroencephalography (EEG), and others. Laboratory abnormalities in patients with HE include those that indicate severe liver disease such as elevated bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase, international normalized ratio (INR), decreased serum albumin level, in addition to possible electrolyte disturbances associated with portal hypertension or the use of diuretics.

Serum and arterial ammonia levels are usually elevated in patients with HE, yet the utility of these tests is controversial due to the fact that these levels are significantly affected by collection techniques and can be falsely elevated if the sample was collected after fist clenching, using tourniquet, or if the sample was not placed on ice.

A number of specialized psychometric and neuropsychiatric tests with a high capacity of detecting minor deficits in mental function are available for the diagnosis and characterization of HE. However, as these tests are labor and time consuming and their reliability is decreased by the learning effect with repetitive administration, they are commonly used for research purposes. Furthermore, a general problem with psychometric tests is that they are not specific to HE and other forms of encephalopathy such as in the case of chronic alcoholism, Wilson disease, and possibly chronic hepatitis C infection can show similar results and findings.

The most frequently applied test is the number connection test (NCT). Furthermore, a battery of five paper-pencil tests were combined together to form the Psychometric Hepatic Encephalopathy Score (PHES) which is capable of
Other tests used in the diagnosis of HE include the inhibitory control test (ICT) which is a computerized test of attention and response inhibition. This test was initially designed to evaluate patients with attention deficit disorder, schizophrenia, and traumatic brain injury. Another test also commonly used in the diagnosis of MHE is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[7]

Techniques that record the evoked potentials from neuronal networks have been used to reflect synchronous volleys of discharges in response to various afferent stimuli. Critical flicker frequency test can be used to evaluate for hepatic retinopathy as a reflection of encephalopathy, as retinal glial cells are also involved in ammonia detoxification by glutamine synthesis and exhibit morphological changes similar to those observed in brain astrocytes.[7]

An important consequence of the application of psychometric tests in patients with cirrhosis was the finding that a significant percentage of patients with apparently normal mental status have a measurable deficit in their intellectual performance, long-term memory, and learning capability. This subclinical or minimal HE affects up to 80 percent of patients with cirrhosis and this abnormality usually resolves following liver transplantation.[13]

**TREATMENT**

It is important to recognize that HE is mostly reversible and that a precipitating cause rather than worsening of hepatocellular function can be identified and successfully treated, thereby leading to resolution on HE in more than 80 percents of patients [Table 1].[7,8] A precipitating factor can often be diagnosed with thorough physical examination and laboratory and imaging tests including complete blood count, renal function tests, serum electrolytes, chest X-ray, urine analysis, blood cultures, and ascitic fluid analysis.[12,41] Infection is the major precipitant of HE in patients admitted to the intensive care unit with positive cultures observed in around 50 percent of these cases.[42]

In addition to targeting the precipitating factor, several therapeutic methods have been used to reduce the ammonia load mainly via inhibiting its production from the GI tract and facilitating its removal. (Algorithm, [Figure 2] ) Synthetic disaccharides (lactulose and lactitol) are widely used in the treatment of HE despite lack of strong scientific evidence that demonstrates their efficacy. Studies have shown these medications are more effective than placebo in improving hepatic encephalopathy but this may not significantly affect patients’ mortality. Approximately 70 to 80 percent.
of patients with HE improve on lactulose treatment. Treatment is usually well tolerated, and the principal toxicity is abdominal cramping, diarrhea, flatulence, and hypernatremia. Interestingly, the nonmetabolized lactose has the same effect of synthetic disaccharides in patients with lactase deficiency.

The nondigestable disaccharides are catabolized by colonic bacteria to short chain fatty acids which lower the colonic pH thereby and lead to the conversion of NH₃ to nonabsorbable NH₄. Furthermore, the cathartic effect of these medications decreases the GI transit time which is frequently delayed in cirrhosis, which in turn increases fecal nitrogen excretion by up to 4 folds. In patients with severe HE and who are at risk for aspiration, oral administration of lactulose can be achieved via a nasogastric tube after endotracheal intubation or it can be substituted for rectal enemas. The therapeutic target for nondigestable disaccharides is to achieve 2-3 soft bowel movements per day. More frequent bowel movements can lead to dehydration and electrolyte imbalance which could worsen HE.

Lowering ammonia levels can be achieved via altering the GI microflora. This has been achieved by the use of various oral antibiotics including neomycin, rifaximin, metronidazole, paromomycin and vancomycin or the administration of nonurease-producing bacteria. Neomycin has been used to treat patients with HE for several decades. The major limiting factor to the use of this antibiotic is its known nephrotoxicity and ototoxicity. Rifaximin is a derivative of rifamycin and has a bioavailability of 0.5% which make it a very safe drug. Studies have shown superiority of rifaximin over lactulose. Rifaximin has been associated with higher response rate, faster effect and less side effects. It has also been shown to improve patients’ quality of life, reduce recurrence rate of overt HE, reduce length of hospitalization and health care costs. Rifaximin has been shown to improve psychomotor abnormalities of MHE.

Alteration of gut flora with probiotics, prebiotics, or synbiotics has been associated with improvement in HE. Probiotics are live microbial feed supplements, prebiotics are nondigestable food ingredients that nourish gut flora, and synbiotics are combinations of these two modalities. Such therapies appear to lower blood ammonia concentrations possibly by favoring colonization with acid-resistant, nonurease producing bacteria. These treatments may result in significant improvement in overt and minimal HE. A study by Bajaj et al. showed reversal of MHE in 70% of patients treated with probiotic yogurt.

Studies have shown that the oral hypoglycemic agent, acarbose, which inhibits alpha glycosidase also inhibits alpha-glucosidases that convert carbohydrates into monosaccharides. This results in increased delivery on polysaccharides into the intestines where they are catalyzed by saccharolytic bacterial flora. This is also associated with inhibition of proteolytic flora that produce mercaptans, benzodiazepine-like substances, and ammonia. The use of acarbose has been shown to lower blood ammonia levels and improve HE in patients with concomitant diabetes mellitus type II.

Ammonia is normally removed by formation of urea in periportal hepatocytes and/or by synthesis of glutamine from glutamate in perivenous hepatocytes. Studies targeting this process have shown mild effect of Ornithine-Aspartate in lowering serum ammonia levels and improving HE. Other studies evaluated the role of sodium benzoate on reacting with glycine to develop hippurate which is a urinary excreted nitrogen waste. Initial results indicated similar efficacy to lactulose.

The benefit of altering the plasma aromatic amino acids (AAA) to branched-chain amino acids (BCAA) ratio in the treatment of HE continues to be unclear. Studies of oral and parenteral administration of BCAA have revealed mixed results thus this treatment should be considered in severely ill patients.
protein-intolerant patients.\textsuperscript{[57]}

Studies have indicated that the GABA-receptor complex may contribute to neuronal inhibition in HE. This complex is the principal inhibitory network in the CNS and consists of a GABA-binding site, a chloride channel, and barbiturate and benzodiazepine receptor sites. The benzodiazepine receptor antagonist flumazenil has shown some success in reversing HE, yet its effect was short-lived.\textsuperscript{[58,59]}

Initial studies on animal modules of liver failure have shown an inverse correlation between Zinc levels in brain tissue and severity of HE.\textsuperscript{[60]} Despite anecdotal reports, human studies have not shown a strong evidence that Zinc supplementation improves or prevents HE.\textsuperscript{[61-63]}

Major spontaneous portosystemic shunts should be suspected in cases of refractory HE when a precipitating factor can not be identified. Several reports have shown that ocluding such shunts may improve HE yet this may result in worsening of portal hypertension, ascites and increased risk for esophageal variceal bleeding.\textsuperscript{[64]}

The current nutritional recommendations for patients with cirrhosis do not advocate for lowering protein intake, as malnutrition with resultant muscle wasting has been shown to worsen HE as the muscles are known to participate in lowering serum ammonia levels by converting it to glutamine.\textsuperscript{[65]} In patients with refractory HE, vegetable protein based diet may be recommended.\textsuperscript{[57]}

Liver transplantation is indicated for patients with fulminant or subfulminant liver failure associated with HE and is known to significantly improve HE in patients with cirrhosis.\textsuperscript{[2]} Nevertheless, despite its apparent reversibility, after each episode of overt HE, patients will accumulate some irreversible residual neurologic impairment that can be detected by psychometric testing and has been labeled as chronic HE. In addition, irreversible structural changes of the brain have been detected by MRI evaluation of patients with chronic HE.\textsuperscript{[66]} The severity of this residual impairment correlates with the number of episodes of overt HE and when advanced is considered as a contraindication for liver transplantation.\textsuperscript{[67-69]}

Management of HE is associated with high costs to the hospitals, medical system, and society with the highest percentage of these costs being spent on inpatient treatment.\textsuperscript{[27,64]} Reports from Healthcare Cost and Utilization Project (HCUP), a United States national resource of patient-level hospital care data, indicated that more than 45 thousand patients were admitted to the hospital in 2007 with primary diagnosis of HE. The mean length of hospital stay was 5.5 days and the mean charges were around 28 thousand dollars per patient. This resulted in an aggregate charge of about 1.3 billion dollars. Furthermore, these admissions were associated with 2,841 in-hospital deaths reflecting more than 6% mortality rate. In previous studies we have shown that implementing an inpatient treatment protocol for treatment of HE based on a team-work of nurses and physicians results in significant improvement in morbidity and mortality. In addition, these studies showed significantly decreased treatment costs due to shorter in-hospital length of stay and less days spent in intensive care settings.\textsuperscript{[70-72]}

**CONCLUSION**

Cirrhosis and its complications remain a major burden on the healthcare systems worldwide. With the epidemic of metabolic syndrome and the expected dramatic increases in cases of non-alcoholic steatohepatitis induced cirrhosis, managing complications of cirrhosis including HE will cause more economic burden. Despite extensive research and clinical trials, the pathogenesis of HE remains to be further elucidated and more effective treatments are required.

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