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Review Article

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HEPATIC ENCEPHALOPATHY AND IT'S NOVAL TREATMENT MODALITIES

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ABSTRACT

Hepatic encephalopathy is a reversible neuropsychiatric consequence that occurs due to liver damage. Although the exact origin of encephalopathy is still unknown, three elements are known to be involved: portosystemic shunting, metabolic dysfunction and an alteration of the blood–brain barrier. Neurotoxic and neuroactive chemicals produced from the digestive tract, such ammonia, are believed to either bypass the liver through shunts or pass through the diseased liver and travel straight to the brain. Cerebral dysfunction is the outcome. Ammonia is thought to indirectly alter neurotransmission and enhance the blood–brain barrier's permeability, allowing additional neurotoxins to enter the brain. Hepatic encephalopathy can manifest clinically as ranging from a mild lack of awareness and altered mental state to asterixis (liver flap), severe disorientation, and coma. The focus of this review article will be on the most recent epidemiology, pathogenesis, etiology, clinical presentations, pharmacological therapy and non-pharmacological therapy to enhance patients quality of life. Supportive treatment and ammonia-lowering medication are typically used to treat hepatic encephalopathy. In order to prevent dehydration and electrolyte imbalances, maintain proper nutrition, and create a safe environment that lowers the risk of falls or accidents, supportive care is an essential part of treatment. Antibiotics like rifaximin and disaccharides like lactitol and lactulose are essential parts of ammonia-lowering treatment. Some of the newer therapy include glycerol phenylbutyrate, galexanolone, nitazoxanide.

KEYWORDS: Hepatic Encephalopathy, lactulose, rifaximin, nitazoxanide.

INTRODUCTION

A reversible neuropsychiatric consequence of severe liver disease is hepatic encephalopathy. Although the exact origin of encephalopathy is still unknown, three elements are known to be involved: portosystemic metabolic abnormalities, shunting, and changes to the blood-brain barrier. Ammonia and other intestinally generated neuroactive and neurotoxic chemicals are believed to either bypass the liver through shunts or pass through the damaged liver and reach the brain directly.[49] One frequent side effect of liver dysfunction is hepatic encephalopathy (HE), which might include liver cirrhosis and acute liver failure.[1,2,549,50] Up to 40% of individuals with liver cirrhosis experience hepatic encephalopathy (HE), a defining feature of liver failure.[49,50]

The development of encephalopathy linked to cirrhosis and/or portal systemic shunts can occur spontaneously or as a consequence of certain triggering circumstances. Constipation, dehydration, electrolyte imbalances, gastrointestinal bleeding, and several medications are common triggering causes. It is essential to identify and eliminate these triggering variables. The next goal of therapeutic management is to lower the circulation's level of ammonia or other nitrogenous products. By decreasing transit time and increasing the amount of soluble nitrogen produced in the feces, laxative treatment increases the throughput of bowel contents. Lactulose is a non-absorbable disaccharide that reduces the gut's generation of ammonia. Some of the additional treatments being researched for encephalopathy include l-ornithine-l-aspartate (LOLA), and the Flumazenil which is a benzodiazepine receptor antagonist.[49]

ETIOLOGY

A number of factors can cause hepatic encephalopathy (HE), such as renal failure, gastrointestinal bleeding (such as esophageal varices), constipation, infection, non-adherence to medication, excessive protein intake in the diet, dehydration (due to fluid restriction, diuretics,

diarrhea, vomiting, or excessive paracentesis), electrolyte imbalance, alcohol consumption, or use of certain sedatives, analgesics, or diuretics in the context of chronic liver disease.[49,50] Sometimes the formation of a trans jugular intrahepatic portosystemic shunt is followed by hepatic encephalopathy.[49,50]

EPIDEMIOLOGY

Hepatic Encephalopathy is a consequence of advanced liver disease, which can be acute or chronic (e.g., 30-45% of patients with cirrhosis, 24–53% of patients with TIPS).[49] In the US, there are 7–11 million cases of HE that are common, and every year, about 150,000 new cases are diagnosed. About 20% of individuals who receive a new diagnosis have cirrhosis. Nearly 60% of cases involve chronic hepatitis C, either by itself or in conjunction with liver disease caused by alcohol.[1,2,49]

PATHOPHYSIOLOGY

Pathophysiological mechanism and correlate of HE is the neurotoxicity of ammonia in the brain, either due to increased production or impaired excretion of ammonia.[49,50] Ammonia producing sites in the body include; small intestine, large intestine and kidneys. When food protein is broken down by urease-producing bacteria in gastrointestinal tract, ammonia is created and enterocyte glutaminase's hydrolysis of glutamine.[3,4,5,6] The proximal tubular cells in the kidneys use glutamine to produce ammonia, with bicarbonate being a byproduct. Alteration in the ammonia production at these sites may occur due to various mechanisms includes; gastrointestinal bleeding, hypovolemic states, over-diuresis, hypokalemia, acidosis, and excessive protein intake. The primary location of ammonia catabolism in the liver is through the urea cycle (Krebs-Henseleit cycle), which transforms ammonia into water-soluble Urea. Urine and the intestine are the next routes via which the produced urea is eliminated.[49,50] Because of hepatocellular damage, the liver's ability to detoxify ammonia is diminished or shunting, the systemic circulation's ammonia levels rise. Due to increased protein intake, dysregulation of glucocorticoid hormones, acid-base and potassium imbalance, and increased protein intake, the kidneys also play a role in decreased ammonia excretion. Moreover, skeletal muscle contributes to the detoxification of ammonia by means of glutamine synthase, which changes ammonia into glutamine. As a result, sarcopenia—a frequent side effect of cirrhosis—may have a negative impact on HE. Due to the elevated amount of ammonia in the systemic circulation causes neuronal dysfunction.[54,55]

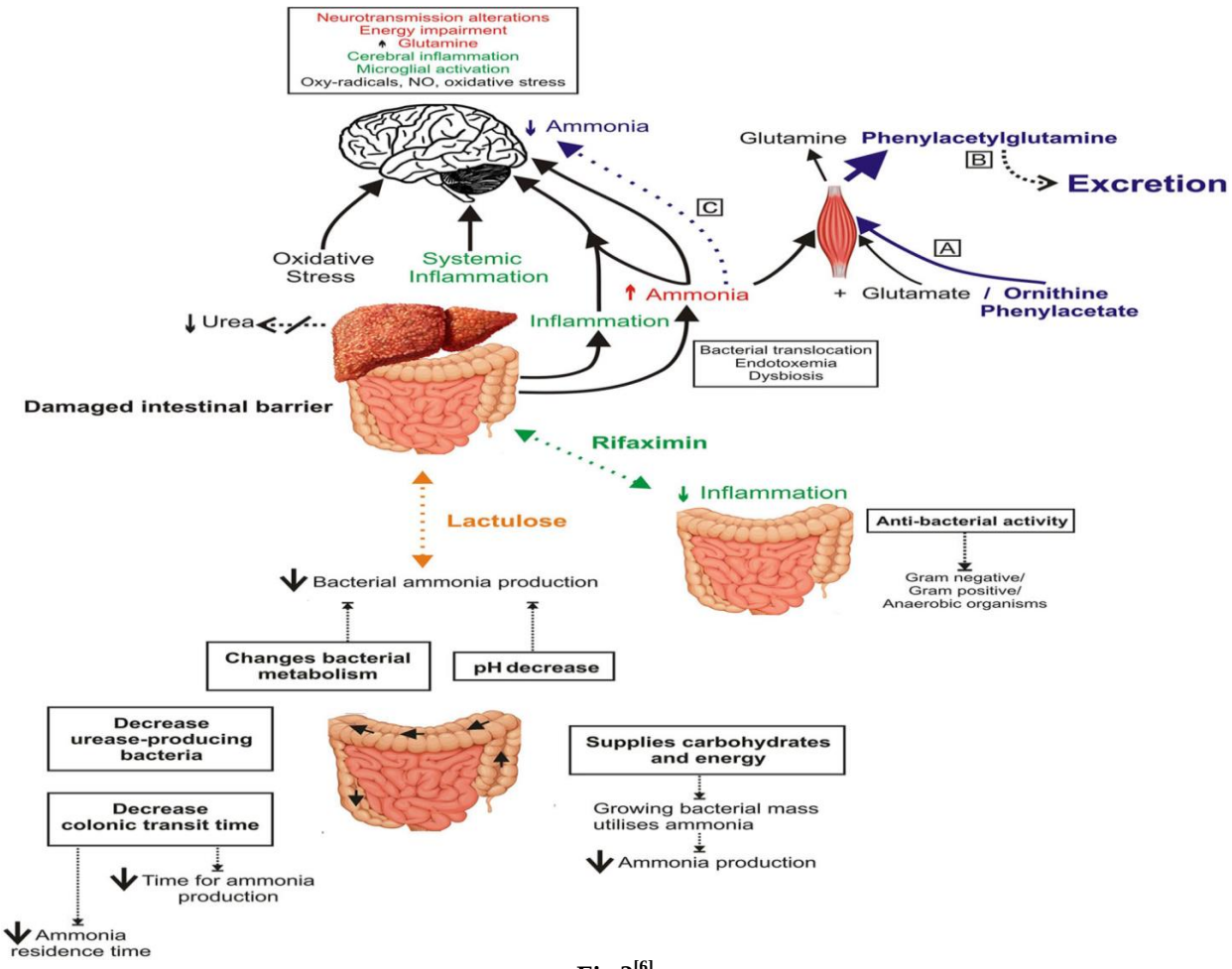

Fig 2[6]

CLASSIFICATION OF HEPATIC ENCEPHALOPATHY

Modified Parsons-Smith or West Haven criteria for HE[10]

Grade 0: No abnormality detected (minimal hepatic encephalopathy)

Grade 1: Trivial lack of awareness, Euphoria or anxiety, Shortened attention span, Impairment of addition or subtraction

Grade 2: Lethargy, Disorientation for time, Obvious personality change, Inappropriate behavior

Grade 3: Somnolence to semistupor, Responsive to stimuli, Confused, Gross disorientation, bizarre behavior

Grade 4: Coma, unable to test mental state

CLINICAL PRESENTATIONS

It has the potential to impact your personality and mood. Conduct and self-control, thinking, memory, and focus, sleep patterns, lucidity, and consciousness , motor skills and coordination, independence and self-care skills.[1,4,6,8,49]

CURRENTLY AVAILABLE AND EMERGING THERAPEUTIC AGENTS

PHARMACOLOGICAL THERAPIES

Lactulose and lactitol: These are administered orally or rectally to HE patients in an effort to minimize intestinal absorption by capturing ammonia in the gut. Because there is no hydrolytic disaccharidase in the small intestine, lactulose and lactitol cannot be absorbed. This allows them to enter the colon, where the colonic flora ferments them bacterially, acidifying the luminal contents in the process. Because of this acidity, ammonia (NH3) is changed into the non-absorbing ammonium (NH4+), which traps ammonia inside the colon and causes it to be expelled in feces.[2,10,50,51] Lactitol and lactulose are non-absorbable disaccharides(NAD) that are advised as a first-line treatment for HE.[1,2,6,8,9] Compared to lactulose, lactitol, a second-generation NAD, has been shown to be more efficacious and to have better tolerability; nevertheless, a Cochrane review revealed that in contrast to lactulose, it had no positive benefits.[1,2,6,8,9] Diarrhea, nausea, and bloating are possible side effects of lactulose treatment. Vomiting and diarrhea may result in changes in electrolytes, and even worsen HE.[8,9]

L-ornithine L-aspartate (LOLA): LOLA is a blend of natural amino acids that are processed by periportal and perivenous hepatocytes, which use L-ornithine as both a substrate and an activator of carbamoyl phosphate synthetase, the urea cycle's rate-limiting enzyme. Through the enzyme glutamine synthetase, LOLA promotes the synthesis of glutamine, a non-toxic ammonia transporter, and increases the activity of the urea cycle, a pathway that transforms ammonia into urea, a less toxic compound that can be eliminated in urine. LOLA also increases glutamine synthesis in skeletal muscle, which aids in the removal of ammonia. In Europe, LOLA is often used and accessible for the treatment of HE. It isn't available in the USA, though. Although the Food and Drug Administration has not approved intravenous LOLA, the AASLD 2014 guideline suggests it as a substitute or supplemental therapy for HE is not improving with traditional treatment.[2] Up to 18 grams of L-ornithine-L-aspartate per day for up to six months may be considered safe. In general, people tolerate it well.[1,2,6,26]

Rifaximin: Traveler's diarrhea, irritable bowel syndrome (IBS), and hepatic encephalopathy in end-stage liver disease are among the gastrointestinal and liver conditions for which Rifaximin-α, an oral antibiotic of the rifamycin class that targets the gut, has broad-spectrum activity against both Gram-positive and Gram-negative bacteria.[11] The antibiotic rifaximin only acts in the gut, where it inhibits the flow of ammonia into the bloodstream and the synthesis of ammonia by the gut bacteria. It is not absorbed into the bloodstream. Hepatic encephalopathy sufferers will benefit from this effect.[12,14] Combining rifaximin and lactulose not only prevents future relapses but also improves hepatic encephalopathy, lowers the chance of death, and lowers the risk of side effects.[14] Adverse events includes fluid retention in the arms and legs, nausea, insomnia, anemia, pruritis, ascites, increased ALT levels, constipation, dizziness, diarrhea.[14] Usual adult dose for hepatic encephalopathy is 550mg orally twice a day.[21,22]

Naloxone: Supplementing the traditional treatment for hepatic encephalopathy with ornithine aspartate plus naloxone combination therapy provides better therapeutic outcome than traditional treatment alone.[23] Several studies also provide information regarding to the use of naloxone alone in hepatic encephalopathy.[24,25]

Branched chain amino acids: Branched -chain amino acids (BCAAs) are suggested as a standard treatment by some because they may reduce hepatic encephalopathy by aiding skeletal muscle in blood detoxification.[2] Impaired liver function and portosystemic shunts are the causes of the rise in blood ammonia. By absorbing plasma ammonia and converting α-ketoglutarate to glutamate and then glutamate to glutamine using the enzymes glutamate dehydrogenase and glutamine synthetase, skeletal muscle plays a crucial role in extrahepatic ammonia detoxification. For every α-ketoglutarate molecule, two moles of ammonia are eliminated. When ammonia levels in liver cirrhosis patients rise, so does muscle uptake of plasma BCAAs, indicating that BCAAs are crucial for muscle ammonia detoxification and may help prevent HE.[28,29] Usual dose is 11- 57 g/day. BCAAs can affect the blood sugar level, and is dangerous for people with diabetes and undergoing surgery. And also cause stomach issues such as nausea, bloating, diarrhea.

Nitazoxanide: Nitazoxanide can be used to improve the brain health and quality of life of the patient. It can be used as an alternative for rifaximin. Nitazoxanide is an

antiparasitic drug and is a novel thiazolide that selectively targets intestinal tract anaerobes in addition to other protozoa and helminths. That is supplied orally, with a high bioavailability and good tolerance.[27] The same effectiveness on HE as usual treatment was demonstrated by administering 500 mg of NTZ twice a day for seven days. Even so, it did not lead to a significant drop in serum ammonia levels, but it did dramatically lower the CHESS score and improve mental health.[27]

Ornithine phenylacetate: Studies provide evidence of use of ornithine phenylacetate in treating HE[30] In patients with cirrhosis, ornithine phenylacetate (OP), a new ammonia scavenger, reduces ammonia levels without affecting the stomach (i.e., by a separate route). Because L-ornithine increases glutamine synthetase activity, body muscle converts circulating ammonia to glutamine. After that, glutamine and phenylacetic acid (PAA) are conjugated to create phenylacetylglutamine, which is eliminated in the urine without producing additional ammonia. OP could be safely administered and lower plasma ammonia levels in cirrhosis patients, according to three early phase studies.[35,36] The starting OP dose was 0.138 g/h, which was raised to 0.275 g/h after 12 hours and to 0.416 g/h after 24 hours. If patients did not meet predetermined stopping criteria, the dose was gradually increased.[30,31]

Albumin: According to new research, oxidative stress and systemic inflammation may contribute to the onset of HE. Growing interest in using human albumin to treat and prevent HE in decompensated patients is a result of recent discoveries of its anti-inflammatory qualities.[32,33]

AST-120: The synthetic activated carbon microsphere known as AST-120 has a high nonspecific adsorptive capacity and a wide surface area. Its restricted gastrointestinal absorption further enhances its capability to trap hepatotoxins and neurotoxins in the gut.[26,33]

Acetyl-L-carnitine: Acetyl-L-carnitine reduces blood ammonium levels[36] Acetyl-L-carnitine is an ester of L-carnitine and acetate that is synthesized in the human brain, liver, and kidney by the enzyme acetyl-L-carnitine transferase. Through two mechanisms, acetyl-L-carnitine may be a useful treatment for patients with hepatic encephalopathy: first, as urea genesis increases, blood and brain ammonium levels decrease; second, acetyl-L-carnitine, which is transported across the blood–brain barrier and accumulates in the cerebral spinal fluid and brain, facilitates the uptake of acetyl-coenzyme A (CoA) into the mitochondria during fatty acid oxidation, increases the production of acetylcholine, and stimulates the phospholipid protein and membrane synthesis. All of these processes might offer a source of substrate for the synthesis of cellular energy, limiting excessive death of neurons.[36]

Glycerol phenylbutyrate (GPB): Glycerol phenylbutyrate (GPB) reduces ammonia by offering a different route for the excretion of waste nitrogen in the form of phenylacetyl glutamine, which is eliminated in urine, as opposed to urea.[38,39] Glycerol phenylbutyrate (GPB) contains 3 phenyl butyric acid molecules that are metabolized into phenylacetic acid. When glutamine and phenylacetic acid combine to generate PAGN, ammonia is contained and safely eliminated in the urine. Currently approved as an alternate treatment for hyperammonemia in people with abnormalities of the urea cycle, GPB has also been investigated as a possible treatment for HE.[37] Usual dose is 5 to 12.4 g/m^2/day.[37,38]

Benzodiazepine antagonists(Flumazenil): Flumazenil is a benzodiazepine antagonist. Flumazenil benefits by patients temporarily alleviating the cirrhosis-induced hepatic encephalopathy. Although flumazenil cannot be advised for routine therapeutic usage, it may be taken into consideration for individuals with hepatic encephalopathy and chronic liver disease.[45] People with hepatic encephalopathy may benefit from flumazenil, a medication that modifies its effects on these specialized cells by acting on one of the GABA receptors in the brain. It must be administered intravenously, and its effects wear off after a few hours.[40] Usual dose include0.4 – 1mg.

Golexanolone: The purpose of golexanolone is to restore normal function to receptors that impede brain activity.[41] Golexanolone is a novel small molecule GABA-A receptor-modulating steroid antagonist.[42] Golexanolone is a drug which directly targets CNS. Golexanolone enters the CNS and reverses the inhibitory effects of neuroactive steroids on brain function in humans. It normalizes an elevated GABAergic tone, independent of ammonia. It improves cognitive function. Usual dose includes 10, 40 or 80 mg BD.[41,42]

Polyethylene glycol: PEG is effective for the treatment of hepatic encephalopathy. It is an osmotic laxative. Like lactulose PEG is also used for the excess ammonia excretion from the gut. It prevents the reasorption of ammonia from the gut.[44] PEG can minimize hospital stays without increasing the rate of side effects and result in faster HE resolution over the first 24 hours.[45,46] Dose should be adjusted according to the need of the individual and the ammonia level should be properly monitored.[44,46]

ZINC: Zinc is involved in numerous enzymatic processes in the typically functioning liver, including the activation of ornithine transcarbamylase and glutamate dehydrogenase, as well as the urea cycle and glutamine synthetase cycle, respectively. Zinc is an essential co-factor needed for several enzymatic reactions involved in ammonia metabolism. ACTION: A lower incidence of HCC, a less severe and clinically significant HE, a lower incidence of SBP, and an increase in the quality of life of

patients are only a few of the numerous potential positive benefits of zinc replacement that have been reported.[43] Zinc deficiency can cause HE by impairing the conversion of ammonia to urea. Zinc supplements can help restore zinc levels and improve the conversion of amino acids to urea.[43]

NONPHARMACOLOGICAL THERAPIES

Probiotics: In the treatment of HE, probiotics alter gut flora by reducing the number of pathogen bacteria, acidifying the intestinal mucosa, reducing ammonia production and absorption, altering gut permeability, lowering endotoxin levels, and altering short-chain fatty acid production.[1,3,6,17,49]

Fecal microbiota transplantation (FMT): Major aim of this method is to restore the balanced gut microbiome, which can reduce the ammonia production.[50] It aims to introduce healthy gut bacteria from a donor By restoring the integrity of the intestinal barrier, fecal microbiota transplantation (FMT) can decrease ammonia synthesis by changing the composition of the gut microbiota to a taxon deficient in urease, decrease ammonia intake, and boost ammonia clearance by enhancing liver function.[48]

Portosystemic shunt embolization: Patients who are not treated medically may have significant portosystemic shunts (PSSs), which could be targets for treatment. Using interventional radiology to close off an aberrant blood vascular connection known as a "portosystemic shunt" in a patient suffering from hepatic encephalopathy.[47]

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