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"MECHANISTIC PERSPECTIVES ON HEPATIC ENCEPHALOPATHY: THE IMPACT OF AMMONIA ACCUMULATION, NEUROINFLAMMATION AND ASTROCYTE DYSFUNCTION"

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Abstract:

Hepatic encephalopathy (HE), a neuropsychiatric disorder mainly caused by liver failure, leading to impaired detoxification of toxins like ammonia. Elevated ammonia crosses the blood-brain barrier, causing astrocyte swelling, brain edema, and disrupted neurotransmission, which impair neuronal function. Disease progression is also driven by oxidative stress, neuroinflammation, and mitochondrial dysfunction that damage neural cells and impair energy production. Experimental models have helped identify key pathogenic pathways and potential treatments, including antioxidants and strategies to preserve mitochondrial health. Central to HE are disturbances in neurotransmitters such as glutamate and GABA, along with activation of microglia and astrocytes that amplify inflammation and neural injury. Astrocyte swelling due to excess glutamine from ammonia detoxification contributes to brain edema and neurological symptoms. Early diagnosis and a comprehensive approach targeting ammonia reduction, neuroprotection, and inflammation are essential, with ongoing research providing optimism for the development of better treatments to enhance patient results.

Keywords: Hepatic Encephalopathy, Ammonia, Glutamate, Neuroinflammation, Oxidative Stress

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INTRODUCTION:

Hepatic Encephalopathy (HE) is a complex and potentially life-threatening neuropsychiatric disorder that arises as a repercussion of both acute and chronic liver diseases. Its intensity can limit from subtle cognitive disturbances to profound coma, making it a significant health concern worldwide[1]. The condition may cause a substantial burden to the affected individuals and pose the potential for irreversible neurological damage[2].

Hepatic encephalopathy results from insufficient liver function by the accumulation of neuroactive hypoglycaemic intestinal contaminants and toxins that cause temporary dysfunction in brain function due to progressive acute and chronic liver disease. Liver can convert toxic constituents into nontoxic constituents[3].

The hallmark features of HE include notable personality changes, cognitive impairment, confusion, and a progressive decline in consciousness levels. These symptoms primarily result from the accumulation of neurotoxic substances, particularly ammonia, in the bloodstream and brain[4,5].

Symptoms may involve difficulties with attention, disrupted sleep patterns, muscular coordination issues, and can escalate to stupor and coma. In cases of acute liver failure, seizures may also occur. Despite the fact that many studies have been accomplished over the years, the precise biological processes responsible for HE are not yet thoroughly perceived[6].

The symptoms can be classified according to severity grades:

- Minimal HE (grade 0): sleep disturbance, slight attention deficits •
- HE grade 1: mild confusion, mood swings, anxiety, difficulty in motor skills, sleep during the day, and awakening at night.
- HE grade 2: personality change, lethargy. Disorientation in time, slurred speech.
- HE grade 3: slow thinking, sluggish movement, loss of general awareness, severe confusion, involuntary twitching.
- HE grade 4: coma stage[7]

Etiological Factors

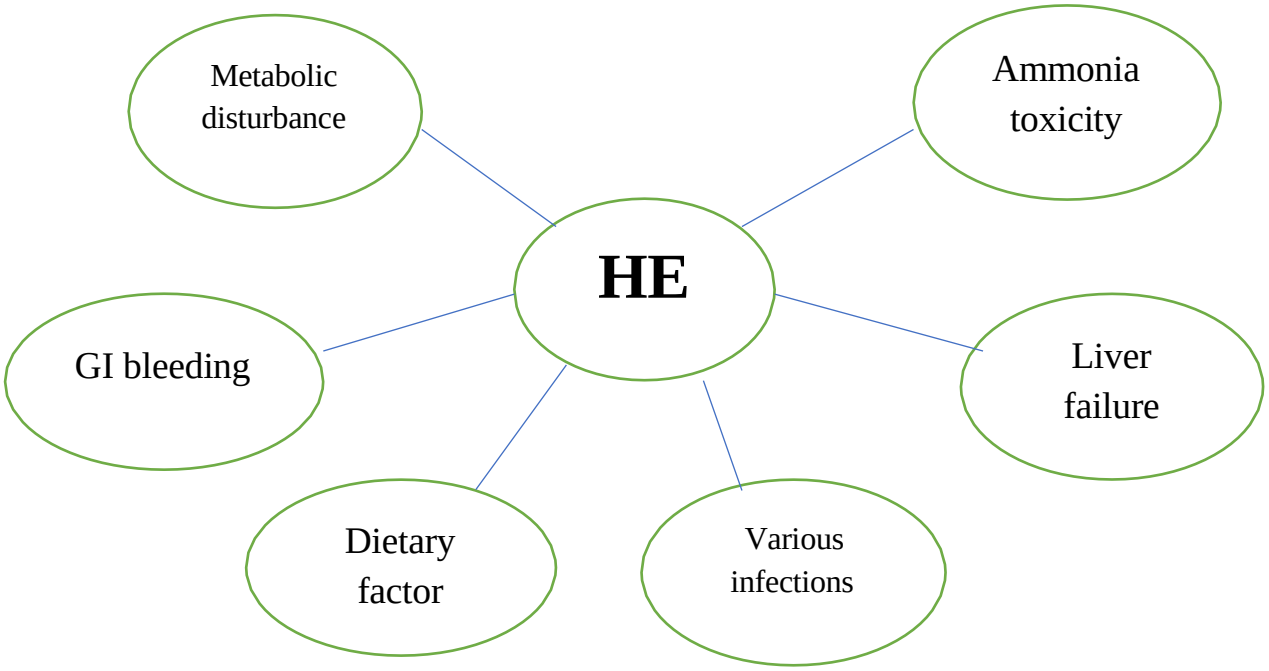

Figure: 1 Diverse causes spurring HE[8]

Thioacetamide (TAA) is widely regarded as a valuable chemical agent used in experimental research to induce hepatic encephalopathy (HE), a complicated neuropsychiatric condition linked with severe liver dysfunction[9]. By administering TAA to laboratory animals, Scientists are able to create frameworks that accurately replicate the clinical and pathological characteristics of both acute and chronic HE observed in humans. These models are instrumental in studying the underlying mechanisms of liver failure, neurotoxicity, and associated neurological impairments, thereby facilitating the development of potential therapeutic interventions[10].

Once metabolized in the liver, TAA is changed into transient reactive species that initiate a cascade of oxidative imbalance within hepatic cells. This oxidative assault damages vital cellular components such as proteins and lipids, impairing normal cellular functions[11]. The resulting oxidative injury compromises mitochondrial integrity, disrupting energy production and promoting cell death. Additionally, damage to cell membranes leads to increased permeability, further exacerbating cellular dysfunction[12]. Collectively, these processes contribute to liver tissue deterioration and the systemic effects that underpin the development of hepatic encephalopathy, making TAA a crucial tool in hepatological research[13].

Carbon tetrachloride (CCl4) is also extensively utilized in experimental models to induce hepatic encephalopathy because of its strong hepatotoxic properties. Upon administration, CCl4 is primarily metabolized within the liver by enzyme cytochrome P450 system, metabolizes it into rapidly reactive free radicals notably the trichloromethyl radical (•CCl3)[14]. These reactive species initiate a chain reaction known as lipid peroxidation, where they attack the lipid components of hepatocyte membranes. This process damages cell membranes, leading to oxidative stress that trigger liver cell death (necrosis), triggers inflammatory responses, and promotes fibrosis—scarring of liver tissue. As a result, overall liver function becomes impaired[15].

This hepatic impairment hampers the liver's capacity to detoxify harmful substances circulating in the blood, particularly ammonia, a byproduct of protein metabolism. Under normal condition, the liver transforms ammonia into urea, which is subsequently eliminated from the body through the kidneys[16]. However, when liver function is compromised, ammonia accumulates in the bloodstream, a condition called hyperammonemia. Elevated ammonia levels can cross the blood-brain barrier and exert neurotoxic effects[17].

Within the brain, excessive ammonia and other toxins induce swelling of astrocytes (a type of glial cell), disrupt neurotransmitter balance, and promote neuroinflammation[18]. These pathological changes impair neuronal function, leading to the clinical features of hepatic encephalopathy, such as confusion, altered consciousness, and motor abnormalities. Overall, the cascade begins with CCl4-induced liver injury and progresses to neurological dysfunction owing to aggregation of neurotoxins[19].

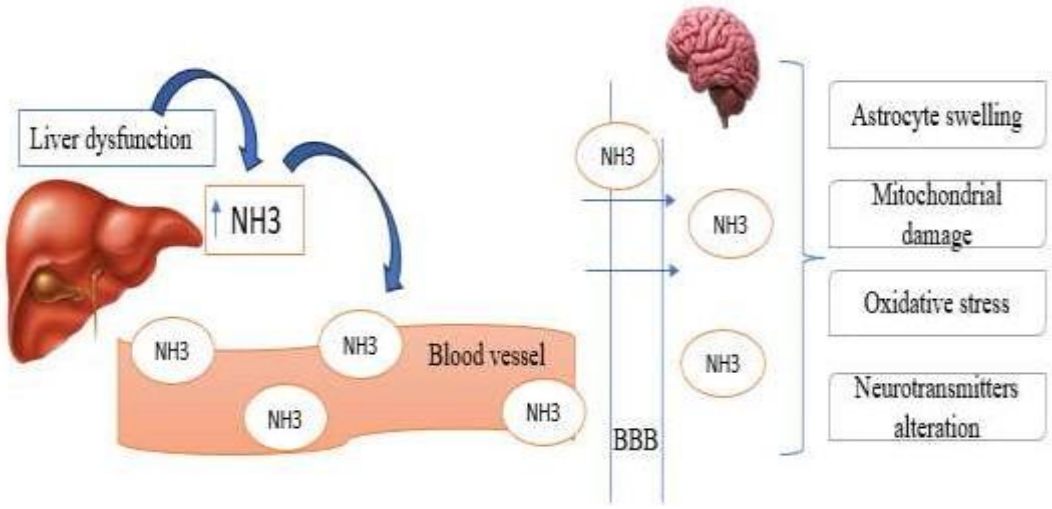

Fig 2: Overall mechanism involved in pathogenesis of HE.

Ammonia, Role in Hepatic Encephalopathy

Ammonia is produced during amino acid breakdown and is normally kept in check by the liver's urea cycle, which transforms toxic ammonia into urea for excretion. In individuals with normal health, blood ammonia concentrations are carefully controlled[21]. However, in liver cirrhosis, the damaged liver can't effectively carry out the urea cycle, leading to an increase in ammonia in the blood, a condition called hyperammonemia. Elevated ammonia levels are a vital aspect in the development of hepatic encephalopathy[21].

Usually, ammonia, which is produced during protein digestion in the intestines, is directed to the liver where it is efficiently converted into urea—a less toxic compound— through the urea cycle. The kidneys subsequently eliminate the urea from the body. However, when liver function is compromised due to injury or cirrhosis, this detoxification process becomes impaired, leading to elevated ammonia levels, a condition known as hyperammonemia. High concentrations of ammonia have multiple detrimental effects on brain function. They can impair cerebral blood flow, leading to alterations in brain perfusion and oxygen delivery[22]. Additionally, ammonia contributes to increased cerebral edema, swelling of brain tissue, oxidative stress and inflammation, alter cerebral perfusion, leading to intensified neurological symptoms. It also disrupts neurotransmitter balance, affecting signalling vital neural pathways required for healthy brain activity[23].

Moreover, ammonia disrupts the structure of the blood-brain barrier, thereby heightening the brain's exposure to harmful toxins and inflammatory agents. Elevated degrees of ammonia in the bloodstream and brain are thought to contribute significantly to the onset of both acute and chronic liver failure. Severe liver disease commonly causes elevated ammonia levels in patients, which may result in hepatic coma, but past research has shown inconsistent correlation between ammonia levels and the potency of hepatic encephalopathy (HE)[24].

Traditionally, diagnosis of HE relies primarily on clinical evaluation and ruling out other causes of altered mental status, with ammonia levels used only to support uncertain cases[25]. Under conditions of elevated ammonia levels, such as those observed in hepatic encephalopathy or liver failure, the brain's immune cells, primarily microglia and astrocytes, become highly activated. This stimulation triggers the generation and emission of pro- inflammatory cytokines, comprising tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6), along with various other mediators involved in inflammation. These cytokines amplify the inflammatory response, resulting in a state of severe neuroinflammation[26].

This inflammatory environment can stress neuronal and glial cells, interfering with the normal activities of cells. and homeostasis. Due to cellular stress and damage, there is an increased release of intracellular molecules like Adenosine 5'-Triphosphate (ATP). ATP, normally confined within cells, acts as a danger-associated molecular pattern (DAMP) when released extracellularly. Its presence in the extracellular space acts as a signaling molecule capable of enhancing activated microglia and other immune cells, thereby perpetuating and amplifying the neuroinflammatory response[27].

Role of neurotransmitters in HE

Glutamate is the main excitatory neurotransmitter in the mammalian CNS. It is essential for numerous brain activities such as processing information, forming and recalling memories, spatial navigation, and sustaining consciousness[28]**.** The process of glutamatergic neurotransmission involves multiple steps: initially, glutamate is released from the presynaptic neuron; once in the extracellular space, it binds to glutamate receptors on the postsynaptic membrane, triggering signal transduction pathways. To prevent excessive stimulation, glutamate is cleared from the synaptic cleft mainly by specialized transporters located in astrocytes[29].

Any disruption in these steps can impair glutamatergic signaling, potentially leading to neurological case, mainly correlated with neurodegenerative diseases. Moreover, excessive glutamate activity, known as excitotoxicity, can cause brain damage, which is also observed in cases of brain ischemia, anoxia, and trauma. Glutamine is vital for both glutamatergic and GABAergic neurotransmission by serving as a shuttle between neurons and astrocytes within the "glutamine-glutamate cycle," an essential pathway for recycling the neurotransmitter glutamate and for GABA synthesis[30].

Additionally, glutamine is vital for ATP production through a series of reactions known as "glutaminolysis." This process involves mitochondrial phosphate-activated glutaminase converting glutamine into glutamate, which is then transformed into α-ketoglutarate by glutamate dehydrogenase. The α-ketoglutarate enters the citric acid cycle, providing NADH for oxidative phosphorylation, ultimately leading to ATP generation. Although glutaminolysis contributes minimally to ATP production in normal cells, it becomes a primary energy source in cancerous

(neoplastic) cells. Furthermore, glutamine is involved in synthesizing glutathione (GSH) by replenishing intracellular glutamate pools, which are fundamental for GSH synthesis[31].

Glutamine serves as a major part in both glutamatergic and GABAergic neurotransmission by serving as a shuttle between neurons and astrocytes within the "glutamine-glutamate cycle," an essential pathway for recycling the neurotransmitter glutamate and for GABA synthesis[32]. Additionally, glutamine is vital for ATP production through a series of reactions known as "glutaminolysis." This process involves mitochondrial phosphate- activated glutaminase converting glutamine into glutamate, which is then transformed into α- ketoglutarate by glutamate dehydrogenase[33]. The α-ketoglutarate enters the citric acid cycle, providing NADH for oxidative phosphorylation, ultimately leading to ATP generation. Although glutaminolysis contributes minimally to ATP production in normal cells, it becomes a primary energy source in cancerous (neoplastic) cells. Furthermore, glutamine is involved in synthesizing glutathione (GSH) by replenishing intracellular glutamate pools, which are required for GSH synthesis[34].

Neuroinflammation and intracellular signalling system in Hepatic Encephalopathy

Hyperammonemia plays a crucial function in the development of hepatic encephalopathy (HE), a complex neuropsychiatric disorder resulting from liver impairment.

Under normal conditions, ammonia generated in the gastrointestinal tract is effectively detoxified: it is either converted into urea by periportal hepatocytes in the liver or utilized in other tissues such as skeletal muscle and the brain, where it contributes to glutamine synthesis. This precise regulation prevents harmful ammonia buildup in the bloodstream[35].

However, when liver function declines, this detoxification process becomes disrupted, leading to an accumulation of ammonia in the blood. Elevated blood ammonia can cross the blood-brain barrier, where it exerts neurotoxic effects, primarily by impairing astrocyte function[36]. Since astrocytes are vital for maintaining neural stability, their dysfunction results in disrupted neurotransmitter balance, brain swelling, and impaired neural communication, ultimately leading to neuronal impairment[37].

Apart from its immediate effects on astrocytes, excess ammonia initiates a series of cellular and molecular reactions that contribute to oxidative damage and neuroinflammation— both of which are key factors in the neurological deficits associated with HE. At the core of this inflammatory process are intracellular signaling pathways involving crucial regulatory proteins such as NF-κB, c-Fos, and MAPKs[38]. These pathways regulate the synthesis of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, which are observed at increased levels in both animal models of acute liver failure and human HE cases. Microglia, the brain's innate immune cells, respond to ammonia-induced stress by activating and releasing these cytokines, thereby intensifying neuroinflammation[39].

The activation of Toll-like receptor 4 (TLR-4) further boosts this response by stimulating NF-κB, leading to heightened inflammation and promoting programmed cell death in neural tissue[40]. This environment of inflammation worsens neuronal damage, disrupts neural circuits, and impairs cognitive abilities. The interplay between ammonia toxicity, microglial activation, cytokine release, and inflammatory signaling creates a detrimental feedback loop that worsens brain swelling, neuronal death, and cognitive decline associated with HE[41].

Understanding this complex interaction between ammonia metabolism, oxidative stress, and nervous system inflammation highlights the need for targeted therapeutic strategies. Approaches that aim to modulate neuroinflammatory responses—such as inhibiting microglial activation, blocking cytokine signaling, or targeting the TLR-4/NF-κB pathways—may offer promising avenues to reduce neurological damage and improve outcomes in hepatic encephalopathy[42].

Oxidative Damage and Mitochondrial Impairment in Hepatic Encephalopathy

Oxidative/nitrosative stress (ONS) occurs when there is an imbalance between the formation of free radicals—such as reactive oxygen species (ROS) and reactive nitrogen species (NOS)—and the body's antioxidant defenses, leading to cellular and tissue damage. ROS are produced through multiple internal biochemical pathways: during aerobic respiration, molecular oxygen is reduced to produce ROS; activated immune cells like phagocytes generate superoxide and hydroxyl radicals as part of their defense mechanisms; and endothelial lining cells generate nitric oxide, a form of NOS involved in vascular regulation. External factors, notably gamma radiation, can further contribute to free radical formation by splitting water molecules, resulting in hydroxyl radicals[43].

Despite the inevitability of free radical generation, the body has evolved sophisticated antioxidant

systems to counteract their harmful effects. These include enzymatic defense, such as SOD, enzymes that transmute oxygen radicals into hydrogen peroxide; catalase, which degrades H2O2 into water and oxygen; and glutathione peroxidases, which reduce peroxides, and non-enzymatic antioxidants like glutathione and uric acid that scavenge free radicals directly[44]. Persistent ONS is critically involved in inducing mitochondrial permeability transition (MPT), a process that compromises mitochondrial integrity and function, thereby contributing to cell injury and death. This mechanism is particularly relevant in the milieu of hepatic encephalopathy (HE), where ongoing oxidative stress exacerbates neuronal and astrocytic dysfunction. Data indicate that radical neutralizers can effectively inhibit MPT in cultured astrocytes exposed to neurotoxic agents such as β-amyloid peptides and ethanol, and can also mitigate ammonia-induced MPT, highlighting the potential therapeutic importance of managing oxidative/nitrosative stress in preventing or alleviating neurodegenerative and liver- related pathologies[45].

During the initial phases of injury, a safeguarding mechanism involving mitochondrial fusion, fission, and mitophagy—regulated by multiple proteins—is activated to restore mitochondrial balance and function[46]. Fusion and fission proteins including mitofusin- 2(MFN2), dynamin-related protein1(Drp1), mitochondrial fission 1 (FIS1), and mitochondrial fission factor(MFF) are crucial cues of HE pathogenesis as their disruption has a major part in hepatic encephalopathy (HE), blood-brain barrier (BBB) dysfunction, along with PTEN-induced kinase-1 (PINK-1) and Parkin, plays a part in mitochondrial quality control—PINK-1 promotes the formation of new, healthy mitochondria, while Parkin facilitates the removal of damaged ones, as part of a coordinated process[47]. Mitophagy is pivotal for upholding mitochondrial performance and promoting overall cellular well-being. Nevertheless, profound mitochondrial damage triggers apoptosis proteinase, hindering mitophagy and evoking apoptosis. Studies suggest that mitophagy depicts a vital part in reducing mitochondrial damage-associated conditions, including hepatic fibrosis and Parkinson's disease[48].

This cascade of events promotes oxidative stress within neural tissues, characterized by an imbalance between free radicals and antioxidant defenses. Oxidative stress, in turn, activates inflammatory pathways, resulting in the increased production of proinflammatory chemokines, which cause neuronal damage and apoptosis (programmed cell death). Overall, these interconnected mechanisms underlie the pathophysiology of HE, illustrating the prominence of managing ammonia levels and protecting brain health in hospitalized individuals with liver disease[49].

Impact of Astrocyte swelling in hepatic encephalopathy

Astrocytes, prevalent Neurons, and other cellular components within the brain, connecting neurons to blood vessels via their end feet, which is a relevant role in forming and maintaining the blood-brain barrier, moreover regulating cerebral blood flow and nutrient delivery. They also surround neuronal synapses, forming the 'tripartite synapse,' where they support energy metabolism through lactate transfer and influence synaptic activity by releasing gliotransmitters, reabsorbing neurotransmitters, and remodelling synapses[50]. Communication between astrocytes occurs through gap junctions, creating the neuroglial vascular unit (NGVU). In pathological conditions, reactive astrocytes may lose their homeostatic functions and become proinflammatory, contributing to neuroinflammation and neurodegeneration. Microglia serve as the brain's primary immune cells, constantly monitoring the environment with their processes to detect pathogens or damage[51].

Upon activation by disease or injury, microglia change shape, produce cytokines, and can induce astrocyte reactivity. They also play roles in synaptic pruning and clearing debris. Astrocytes are unique because they express glutamine synthetase (GS), which allows them to detoxify excess ammonia entering the CNS[52]. In hepatic encephalopathy (HE), "Alzheimer type II" astrocytes—characterized by enlarged cell and nuclear size, prominent nucleoli, reduced cytoplasm, and increased glycogen—are often observed in post-mortem samples. The dysfunction of these cells is largely attributed to hyperammonemia, given the close link between ammonia levels and astrocyte activity[53].

Since peripheral inflammation is involved in HE development and microglia are key mediators of neuroinflammation, it is plausible that peripheral inflammatory signals extend into the brain, with microglia orchestrating this neuroinflammatory response. In HE, astrocyte swelling—a hallmark pathology—is driven by elevated brain ammonia levels, which astrocytes detoxify through glutamine synthetase[54]. Excess ammonia leads to increased glutamine production, an osmotically active molecule that causes water influx into astrocytes, resulting in cellular swelling. This swelling contributes to brain edema, increased intracranial pressure, and impaired neural function, all of which underpin the neurological symptoms associated with hepatic failure. This process

disrupts normal brain homeostasis and is central to the pathology of HE[55].

TREATMENT STATEGIES

1. Lactulose

Lactulose, a nonabsorbable disaccharide, has been a cornerstone in the management of this disease since 1966 and remains highly effective in clinical practice. It works by undergoing fermentation by gut bacteria, producing lactic acid that lowers intestinal pH and reduces ammonia absorption into the bloodstream. This mechanism helps decrease plasma ammonia levels, alleviating neurological and motor symptoms associated with HE. Numerous studies have demonstrated lactulose's capacity to reduce hyperammonemia, improve neurological function, and promote neuroplasticity, particularly at an early point of the condition, despite the fact that underlying mechanisms are not fully understood[56].

Research utilizing animal models, such as rats with bile duct ligation, has demonstrated that elevated ammonia levels are associated with decreased activity in brain regions responsible for anxiety and motor control, partly due to increased GABA receptor activity. Treatment with lactulose has been shown to reduce motor impairments and alter neural activation patterns in these areas. Furthermore, investigations are ongoing into the role of aquaporin-4 (AQP4), a water channel expressed in astrocytes that plays a key role in osmotic balance and is linked to brain edema in hepatic encephalopathy (HE). Understanding how lactulose influences water regulation and neural activity could shed light on its neuroprotective properties and aid in developing strategies to manage brain swelling in HE patients[57].

However, long-term use of lactulose can lead to several adverse effects, including hyponatremia—a dangerous decrease in sodium levels that may cause confusion and seizures.

Severe dehydration is another concern, stemming from lactulose's laxative effect, which can disturb electrolyte balance and cause weakness. Patients often report issues like dry mouth and excessive flatulence, which can impact comfort and adherence to treatment. These side effects underscore the need for alternative therapies that are both safe and effective for HE management[58]. Researchers are actively seeking new medications and approaches that target ammonia reduction or offer neuroprotection with fewer risks. Developing safer treatment options would significantly improve patient outcomes, reduce adverse effects, and enhance overall quality of life. Ultimately, the search for more effective and safer therapies remains a priority in advancing care for individuals with liver-related neurological conditions[59].

2. Rifaximin

Rifaximin is a semi-synthetic antibiotic derived from rifamycin that has become widely recognized as an effective therapy for hepatic encephalopathy (HE). It works by targeting a diverse range of bacteria in the gastrointestinal system, including both gram-positive and gram- negative organisms, as well as aerobic and anaerobic bacteria. By lowering the bacterial load, rifaximin reduces the production of toxins such as ammonia, which significantly contribute to the neurological symptoms associated with HE. A key benefit of rifaximin is its limited absorption into the bloodstream, which keeps its activity confined mainly to the gut. This localized effect makes it suitable for long-term use, especially in patients with liver or kidney dysfunction, as it minimizes systemic side effects and decreases the need for frequent dosage adjustments[60].

Numerous clinical studies have demonstrated that rifaximin can effectively prevent HE episodes from recurring, decrease hospital stays, and improve overall patient health. Moreover, rifaximin is generally well tolerated, with a low rate of adverse reactions. Its safety profile supports its use as a long-term management option, particularly for individuals who cannot tolerate other treatments such as lactulose or who frequently relapse. The combination of its effectiveness and safety has established rifaximin as a valuable medication in the treatment of HE. Research continues to explore its full potential across different stages of liver disease and in combination with other therapies or preventative measures. These investigations aim to refine treatment protocols and enhance the quality of life for patients[61].

CONCLUSION:

Hepatic encephalopathy (HE) is a serious neuropsychiatric condition primarily resulting from liver failure, which diminishes the body's capacity to eliminate harmful substances like ammonia. When ammonia accumulates, it crosses the blood-brain barrier, causing neurotoxicity, swelling of astrocytes, brain edema, and increased intracranial pressure. These changes lead to a spectrum of neurological issues, including confusion, disorientation, and potentially coma. Beyond ammonia buildup, factors such as oxidative stress, neuroinflammation, and mitochondrial dysfunction play critical roles in disease progression by damaging nerve cells, promoting inflammation, and impairing energy production necessary for normal brain activity. These pathological processes fuel a vicious cycle, worsening neural injury and cognitive decline. Animal models using chemicals like thioacetamide and carbon tetrachloride have been pivotal in

understanding these mechanisms, revealing potential targets for therapy, such as antioxidants and anti-inflammatory drugs, to reduce neural damage. Disruptions in neurotransmitter systems, especially those involving glutamate and GABA, further contribute to deficits in cognition and motor control by impairing neural signaling and synaptic function. Additionally, mitochondrial dysfunction and compromised blood-brain barrier integrity permit toxins, inflammatory agents, and immune cells to invade brain tissue, intensifying injury and inflammation. Systemic inflammation originating from the diseased liver extends into the brain, amplifying neuroinflammatory responses and accelerating neural deterioration. Managing HE effectively requires early detection, dietary adjustments, medications to reduce ammonia levels, and treatments to support liver health. Recent research suggests that targeting oxidative stress and neuroinflammation could offer additional benefits, potentially preventing or reversing some brain damage. Protecting mitochondrial function and maintaining the blood-brain barrier are vital strategies to avoid irreversible brain injury and preserve neurological function. A comprehensive approach that combines symptom management with neuroprotective strategies is essential for enhancing patient quality of life and reducing mortality. Ongoing studies of the molecular and cellular pathways involved in HE are crucial for developing innovative and more effective therapies.

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