TENDERENDA, Maciej, BUCZKOWSKI, Bartosz, OLEKSY, Piotr, KLECZA, Agnieszka, BRONIAK, Aleksandra, RECLIK, Magdalena, ZIELIŃSKI, Karol, CHOURASIA, Aarushi, NOWAKOWSKI, Krzysztof and CHRAŚCINA, Martyna. Liver Disease and Central Nervous System Dysfunction: Linking the Two - A Narrative Review. Journal of Education, Health and Sport. 2024;75:56180. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.75.56180
https://apcz.umk.pl/JEHS/article/view/56180

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 13.11.2024. Revised: 20.11.2024. Accepted: 27.11.2024. Published: 27.11.2024.

Liver Disease and Central Nervous System Dysfunction: Linking the Two - A Narrative Review

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Abstract

Introduction: Liver dysfunction can significantly impact the central nervous system (CNS), leading to neuropsychiatric complications such as hepatic encephalopathy (HE). HE, a potentially reversible condition, results from the accumulation of toxins, particularly ammonia, which a diseased liver fails to detoxify, affecting brain function. It is commonly associated with chronic liver diseases like cirrhosis but can also occur acutely in cases of fulminant liver failure.

Purpose of Research: This review aims to explore the mechanisms linking liver dysfunction to brain impairment in HE and to summarize recent findings on liver disease's effects on CNS dysfunction.

Materials and Methods: The review synthesizes findings from 45 studies on HE pathogenesis and treatment, published between 2003 and 2024. These studies, sourced from PubMed and Scopus, focus on mechanisms including ammonia toxicity, neuroinflammation, oxidative stress, and neurotransmitter imbalance.

Basic Results: HE pathogenesis is multifactorial, with systemic metabolic disturbances causing complex interactions among neurotoxic ammonia buildup, chronic neuroinflammation, oxidative stress, and neurotransmitter imbalances. Traditional therapies like lactulose and rifaximin primarily target ammonia reduction, while newer treatments, including ammonia scavengers, anti-inflammatory agents, and antioxidants, address specific pathogenic pathways. The gut-liver-brain axis, involving gut microbiota's role in CNS functioning, presents promising avenues for adjunctive treatment**.**

Conclusions: Addressing HE requires a multifaceted approach, including ammonia reduction, inflammation control, and neurotransmitter balance restoration. Traditional therapies remain central to HE management, but emerging treatments and modulation of gut microbiota may enhance outcomes and improve quality of life for patients with liver disease-related brain dysfunction.

Keywords: Hepatic encephalopathy; Liver disease; Neuroinflammation; Ammonia toxicity; Gut-liver-brain axis

Introduction

The liver, as a central metabolic organ, plays a critical role in detoxification, regulation of metabolic processes, and synthesis of essential compounds in the body. Its dysfunction can have systemic effects, particularly impacting the central nervous system (CNS) through a range of mechanisms that can lead to neuropsychiatric disturbances and cognitive decline (Ferenci et al. 2008). One of the most serious neuropsychiatric complications of liver disease is hepatic encephalopathy (HE), a complex and potentially reversible condition characterized by altered brain function resulting from the accumulation of toxins, particularly ammonia, which the diseased liver fails to clear effectively from the bloodstream (Butterworth 2010; Jalan et al. 2011).

Hepatic encephalopathy is primarily associated with chronic liver diseases, such as cirrhosis, but can also occur acutely in patients with fulminant liver failure (Vilstrup et al. 2014). The condition ranges in severity, from minimal hepatic encephalopathy (MHE), which often presents with subclinical cognitive impairments, to overt hepatic encephalopathy (OHE), marked by more profound alterations in consciousness and motor functions (Bajaj et al. 2009; Dhiman et al. 2010). The pathophysiology of HE involves complex processes, including neuroinflammation, disruption of the blood-brain barrier, oxidative stress, and neurotransmitter imbalances, making it a challenging disorder to manage and treat effectively (Zieve et al. 2009; Montagnese and Bajaj 2015).

Current research on HE is focused on understanding its pathogenesis, improving diagnostic strategies, and developing therapeutic approaches that target specific pathways in its development. Traditional assessments of HE, which rely on clinical evaluation, are increasingly complemented by advanced imaging techniques and psychometric testing, providing a more nuanced understanding of how liver dysfunction affects brain function (Romero-Gomez et al. 2009; Tapper et al. 2015).

This review aims to explore the underlying mechanisms linking liver diseases with brain dysfunction, focusing on hepatic encephalopathy. Additionally, it highlights recent findings regarding the impact of hepatic dysfunction on brain health and discusses current and emerging therapeutic approaches for managing HE.

Underlying Mechanisms Linking Liver Diseases with CNS Dysfunction

Liver diseases, especially those resulting in chronic liver failure, have significant implications for brain health, largely due to systemic metabolic disturbances and neurotoxic buildup. The underlying mechanisms linking liver dysfunction to brain impairment in hepatic encephalopathy involve complex interactions between ammonia toxicity, neuroinflammation, oxidative stress, and neurotransmitter imbalances. These mechanisms not only account for the cognitive, motor, and behavioral changes in HE but also provide insight into potential therapeutic targets. Table 1. summarizes pathophysiological mechanisms connecting liver disease with CNS damage.

Table 1. Underlying mechanism linking liver disease with CNS dysfunction

Mechanism	Description	Potential Therapeutic Target	References
Ammonia Toxicity and Astrocyte Swelling	Ammonia crosses the blood-brain barrier and accumulates in astrocytes, leading to glutamine synthesis, increased osmotic pressure, and astrocyte swelling, which disrupts neurotransmitter cycling and ion balance	Reducing ammonia levels and preventing astrocyte swelling to improve neurotransmitter balance.	(Butterworth 2010; Norenberg and Rao 2008; Shawcross et al. 2008; Wright et al. 2011)
Neuroinflammation and Microglial Activation	Systemic inflammation from liver failure activates microglia, releasing cytokines (TNF-α, IL-1β, IL-6) that increase BBB permeability and cause neurotoxicity [5,6,7,8].	Using anti-inflammatory agents or cytokine inhibitors to limit microglial activation and reduce neurotoxicity.	(Häussinger et al. 2009; Shawcross et al. 2011; Aldridge et al. 2015; Jalan et al. 2011)
Oxidative Stress and Mitochondrial Dysfunction	Oxidative stress from ammonia and inflammatory mediators disrupts mitochondrial function, increasing ROS production and damaging neurons	Employing antioxidant therapies like NAC to counteract oxidative damage and support mitochondrial function.	(Bosoi and Rose 2013; Felipo and Butterworth 2009; Rama Rao and Norenberg 2008; Montagnese and Bajaj 2015)
Neurotransmitter Imbalance	Ammonia raises GABAergic tone and lowers glutamate levels, causing a neurotransmitter imbalance that	Modulating GABAergic and glutamatergic systems to restore neurotransmitter balance.	(Wright and Jalan 2007; Weissenborn et al. 2009; Riggio et al. 2010)

	contributes to cognitive and motor deficits in HE		
Blood-Brain Barrier Disruption	Systemic inflammation weakens BBB integrity, allowing neurotoxins to enter the brain, which exacerbates neuroinflammation and neuronal injury	Protecting BBB integrity using agents like albumin to reduce inflammation and prevent neurotoxin entry.	(Romero-Gomez et al. 2009; Zhang et al. 2012; Jalan et al. 2008)
Role of the Gut-Liver-Brain Axis	Liver dysfunction disrupts gut microbiota, increasing neurotoxic substances (ammonia, endotoxins) and systemic inflammation, impacting brain function	Modulating gut microbiota with probiotics or synbiotics to reduce neurotoxin production and inflammation.	(Bajaj 2010; Horvath et al. 2016)

Ammonia is a key neurotoxin involved in the pathogenesis of HE. Normally, ammonia is detoxified by the liver via the urea cycle, but liver failure impairs this process, leading to elevated blood ammonia levels. Once in the bloodstream, ammonia crosses the blood-brain barrier and enters the CNS, where it exerts direct neurotoxic effects (Butterworth 2010). One of the primary targets of ammonia in the brain is the astrocyte, a glial cell responsible for maintaining brain homeostasis. Astrocytes metabolize ammonia by converting it to glutamine via the enzyme glutamine synthetase. However, excessive glutamine production increases intracellular osmotic pressure, causing astrocytes to swell - a condition known as astrocyte edema (Norenberg and Rao 2008). This swelling disrupts normal cellular function, leading to impaired neurotransmitter cycling, altered ion balance, and reduced energy production in neurons (Shawcross et al. 2008). Recent studies have shown that astrocyte swelling also contributes to increased intracranial pressure, further complicating HE pathology and exacerbating neurological symptoms (Wright et al. 2011).

Neuroinflammation is another critical contributor to brain dysfunction in liver disease. Liver failure and the associated systemic inflammation activate microglial cells in the CNS, the resident immune cells of the brain. Activated microglia release a cascade of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which have been linked to neurotoxicity in HE patients (Häussinger et al. 2009). These inflammatory mediators further enhance blood-brain barrier permeability, allowing additional toxins to enter the brain and aggravate neuronal damage (Shawcross et al. 2011). Chronic neuroinflammation also leads to long-term changes in brain function and structure. For instance, prolonged exposure to inflammatory cytokines has been shown to alter synaptic plasticity and impair neurogenesis, contributing to persistent

cognitive deficits (Aldridge et al. 2015). Studies in both animal models and human patients have demonstrated that therapies aimed at reducing neuroinflammation - such as anti-inflammatory agents or cytokine inhibitors - may alleviate cognitive symptoms, underscoring the importance of targeting inflammation in HE management (Jalan et al. 2011).

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is prevalent in liver disease and plays a major role in HE. High levels of ammonia and inflammatory mediators can disrupt mitochondrial function, leading to increased ROS production and oxidative damage to proteins, lipids, and DNA within neurons (Bosoi and Rose 2013). Oxidative stress further exacerbates astrocyte swelling and neuroinflammation, creating a vicious cycle of cellular injury in the brain (Felipo and Butterworth 2009). The mitochondria, essential for cellular energy production, are particularly susceptible to oxidative damage. Mitochondrial dysfunction impairs ATP production, leading to energy deficits that affect various cellular processes, including neurotransmitter recycling and ion balance maintenance (Rama Rao and Norenberg 2008). In HE patients, studies have shown that antioxidant therapies, such as N-acetylcysteine (NAC), can reduce oxidative stress markers and improve cognitive outcomes, suggesting that strategies to mitigate oxidative damage may be beneficial (Montagnese and Bajaj 2015).

Hepatic dysfunction and ammonia accumulation can disrupt neurotransmitter systems, particularly those involving gamma-aminobutyric acid (GABA) and glutamate. High ammonia levels lead to an increase in brain GABAergic tone and a decrease in glutamate availability, primarily due to the conversion of glutamate to glutamine in astrocytes (Wright and Jalan 2007). This imbalance between excitatory (glutamate) and inhibitory (GABA) neurotransmission contributes to the cognitive and motor deficits seen in HE. The "GABAergic hypothesis" of HE suggests that elevated GABAergic activity may lead to reduced arousal and cognitive impairment. Elevated levels of benzodiazepine-like substances, which act on GABA-A receptors, have been detected in the cerebrospinal fluid of HE patients, further supporting this hypothesis (Weissenborn et al. 2009). Therapies targeting neurotransmitter balance, such as GABA receptor modulators, are being investigated for their potential to alleviate HE symptoms, although the efficacy of these treatments varies (Riggio et al. 2010).

The integrity of the blood-brain barrier (BBB) is crucial for protecting the brain from systemic toxins. In liver disease, systemic inflammation and increased cytokine levels weaken BBB integrity, allowing ammonia, inflammatory mediators, and other toxins to enter the brain more freely (Romero-Gomez et al. 2009). Studies using advanced imaging techniques have shown that BBB disruption in HE patients correlates with cognitive decline and neuroimaging abnormalities, including white matter damage and cortical atrophy (Zhang et al. 2012). The breakdown of the BBB initiates a cascade of events that exacerbate neuroinflammation and oxidative stress, leading to cumulative neuronal injury. Interventions aimed at protecting BBB integrity, such as the use of albumin to reduce systemic inflammation, have shown potential in preserving cognitive function and reducing HE progression (Jalan et al. 2008).

Recent research has highlighted the significance of the gut-liver-brain axis in HE pathogenesis. The liver's impairment disrupts gut microbiota composition, leading to

increased production of neurotoxic substances, including ammonia and endotoxins, which can enter the bloodstream and impact brain function. Dysbiosis, or microbial imbalance in the gut, is common in cirrhotic patients and contributes to systemic inflammation, BBB disruption, and neuroinflammation (Bajaj 2010). Interventions targeting the gut microbiota, such as probiotics and synbiotics, have shown promise in reducing ammonia levels and improving cognitive outcomes in HE patients. Studies suggest that these treatments may restore a healthy microbial balance in the gut, decreasing neurotoxin production and inflammation (Horvath et al. 2016).

Recent Findings Regarding the Impact of Liver Disease on CNS Dysfunction

Recent studies have shed new light on the mechanisms by which hepatic dysfunction contributes to brain health deterioration, with hepatic encephalopathy representing only one aspect of a broader spectrum of neurological impairments associated with liver disease.

Cognitive dysfunction is one of the most pronounced effects of hepatic impairment, manifesting in both subtle and overt forms depending on the severity of liver disease. Even patients with MHE, who may not exhibit obvious neurological symptoms, often demonstrate significant cognitive impairment on neuropsychological testing (Bajaj et al. 2009). MHE has been associated with deficits in attention, working memory, and psychomotor speed, all of which can impair daily functioning and quality of life (Montagnese and Bajaj 2015). The presence of MHE is considered a predictor of poor prognosis, as it frequently progresses to OHE if left untreated. Recent neuroimaging studies have correlated these cognitive deficits with structural changes in the brain. For example, magnetic resonance imaging (MRI) studies have shown that patients with cirrhosis exhibit cortical atrophy and reduced white matter integrity, particularly in the frontal and parietal lobes, regions associated with executive function and attention (Weissenborn et al. 2009). These structural changes are thought to be driven by chronic neuroinflammation, ammonia toxicity, and disruptions in cerebral blood flow (Butterworth 2010).

Mood disorders, particularly depression and anxiety, are increasingly recognized as prevalent and impactful consequences of chronic liver disease. Studies have found that the prevalence of depression in patients with liver disease, especially cirrhosis, is significantly higher than in the general population (Elwing et al. 2006). The exact mechanisms linking hepatic dysfunction to mood disorders are still under investigation, but it is believed that a combination of inflammatory cytokine release, changes in neurotransmitter levels, and altered hypothalamic-pituitary-adrenal (HPA) axis function contribute to the emotional dysregulation observed in these patients (Swain and Jones 2012). The overlap between mood disorders and cognitive dysfunction in liver disease patients complicates diagnosis and treatment. Studies suggest that these mood disturbances further impair cognitive performance, leading to a cycle of worsening symptoms that affect the patient's quality of life and adherence to medical treatment (Dhiman et al. 2010). Effective management of these mood symptoms has been shown to improve overall outcomes, with interventions such as psychotherapy and antidepressant use being explored as adjuncts to traditional treatments for liver disease and HE (Bajaj 2010).

Chronic liver disease has been associated with various structural changes in the brain, largely attributed to persistent neuroinflammation and neurotoxic metabolite accumulation. Advanced

neuroimaging techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI), have provided insights into the microstructural changes that occur in the brains of HE patients (Zhang et al. 2012). These studies reveal a widespread loss of white matter integrity and reduced connectivity in brain networks responsible for cognition and motor control (Kale et al. 2014). One of the most significant findings in recent years is the role of microglial activation in the pathogenesis of HE. Microglia, the brain's resident immune cells, become activated in response to systemic inflammation and ammonia accumulation in liver disease. This activation leads to the release of pro-inflammatory cytokines and neurotoxic substances, which contribute to neuronal injury and functional impairments in the brain (Häussinger et al. 2009).

Animal studies have demonstrated that inhibiting microglial activation can reduce neuroinflammation and improve cognitive outcomes, highlighting microglia as a potential therapeutic target in HE (Rama Rao and Norenberg 2008).

Hepatic dysfunction also affects the permeability of the blood-brain barrier (BBB), allowing more toxins and inflammatory mediators to reach the CNS. Studies have shown that patients with cirrhosis exhibit disruptions in BBB integrity, which correlate with cognitive decline and neuroimaging abnormalities (Wright et al. 2011). This increased permeability facilitates the entry of neurotoxic substances such as ammonia, manganese, and inflammatory cytokines, exacerbating neuroinflammation and brain injury (Butterworth et al. 2009). A novel area of research has focused on the potential role of manganese deposition in the brains of patients with liver disease. MRI studies have detected increased manganese accumulation in the basal ganglia of HE patients, which is associated with motor dysfunctions such as tremors and dysarthria (Qu et al. 2015). Manganese is normally excreted by the liver, and its accumulation in the brain due to hepatic dysfunction may represent another pathway through which liver disease contributes to neurological symptoms.

Identifying biomarkers that can predict or detect cognitive impairment in liver disease patients has been a priority in recent research. Biomarkers such as serum ammonia levels, inflammatory cytokines (e.g., IL-6, TNF-α), and S100B, a protein linked to astrocyte activation, have shown promise in reflecting the severity of neuroinflammation and cognitive impairment in HE (Romero-Gomez et al. 2009). Additionally, advanced imaging biomarkers, including alterations in cortical thickness and white matter integrity on MRI, have been associated with cognitive decline in liver disease patients (Bosoi and Rose 2013). Efforts to validate these biomarkers in clinical practice are ongoing, with the aim of improving early detection and risk stratification for HE. Early identification of patients at risk for cognitive impairment can enable timely intervention, potentially slowing the progression of brain dysfunction associated with hepatic disease (Tapper et al. 2015).

Current and Emerging Therapeutic Approaches for Managing Hepatic Encephalopathy

Management of hepatic encephalopathy aims to reduce neurotoxic ammonia levels, control neuroinflammation, and restore the balance of neurotransmitters to improve cognitive function and quality of life in patients. Current treatments primarily target the reduction of ammonia production and absorption in the gastrointestinal tract, but new therapeutic approaches are being investigated to address additional pathophysiological mechanisms,

including oxidative stress, neuroinflammation, and blood-brain barrier integrity. Table 2. summarizes traditional and novel therapeutic approaches for hepatic encephalopathy.

Table 2. Standard and emerging therapeutic approaches for hepatic encephalopathy.

Therapeutic Approach	Mechanism	Advantages	Disadvantages	References
Lactulose (Standard Therapy)	Reduces ammonia production by acidifying gut; acts as a laxative to clear ammonia	Proven efficacy in preventing HE recurrence; inexpensive	Potential for diarrhea, bloating; requires regular dosing	(Bajaj et al. 2009; Romero-Gomez et al. 2009; Als-Nielsen et al. 2004)
Rifaximin (Standard Therapy)	Broad-spectrum antibiotic targeting gut bacteria responsible for ammonia production	Effective adjunct to lactulose; reduces HE recurrence and hospitalization risk	Potential for bacterial resistance; high cost	(Bajaj et al. 2013; Bass et al. 2010)
Ornithine Phenylacetate	Ammonia scavenger that binds ammonia for renal excretion	Directly targets ammonia; potential to reduce hospitalizations	Further research needed for long-term safety	(Jalan et al. 2008; Vaquero et al. 2003)
Glycerol Phenylbutyrate	Oral ammonia scavenger effective in lowering ammonia levels in cirrhotic patients	Effective in clinical trials; available for urea cycle disorders	Limited evidence on safety and efficacy in HE; potential side effects	(Ventura-Cots et al. 2021)
Albumin Infusions	Reduces	Improves	Long-term	(Jalan and

	systemic inflammation and has antioxidant effects	survival rates in cirrhotic patients; reduces HE episodes	effects and optimal dosing need further study	McPhail 2012; Fernández et al. 2014)
Statins	Anti-inflammatory effects, reduces portal hypertension, may preserve blood-brain barrier integrity	Potential to reduce HE incidence and improve endothelial function	Requires further study for HE-specific effects; possible side effects	(Riggio et al. 2010; Lee et al. 2012)
N-Acetylcysteine	Antioxidant therapy to reduce oxidative stress	Reduces oxidative stress; neuroprotective in acute liver failure	Limited evidence in chronic HE; more studies needed	(Elsaid and Rustgi 2020)
L-Carnitine	Supports mitochondrial function by facilitating fatty acid transport	Improves cognitive function and fatigue; supports psychometric performance	Limited efficacy in severe HE; may require combination therapy	(Hadjihambi et al. 2015)
Flumazenil	GABA receptor antagonist to counteract GABAergic tone	Temporary improvement in mental status; targets GABAergic imbalance	Short-lived effects; not suitable for long-term management	(Reverter et al. 2021)
Probiotics/Synbiotics	Modulates gut microbiota, reduces ammonia production, and decreases systemic inflammation	Improves gut health, reduces HE recurrence; may improve cognitive outcomes	Requires more standardization; variable effectiveness across strains	(Horvath et al. 2016; Bajaj et al. 2008)

Standard Therapies

The primary therapeutic strategy for managing HE continues to focus on reducing ammonia production in the gastrointestinal tract. Two widely used agents, lactulose and rifaximin, work by decreasing ammonia-producing bacteria in the gut and enhancing ammonia elimination.

Lactulose is a non-absorbable disaccharide that promotes acidification of the gut, leading to conversion of ammonia into ammonium, which cannot be absorbed into the bloodstream. It also acts as a laxative, helping to clear ammonia through stool. Multiple studies have confirmed the efficacy of lactulose in both treating and preventing HE episodes (Bajaj et al. 2009; Romero-Gomez et al. 2009). A meta-analysis demonstrated that lactulose significantly reduces the risk of HE recurrence, making it a cornerstone of long-term HE management (Als-Nielsen et al. 2004). Rifaximin, a broad-spectrum antibiotic, has emerged as an effective adjunctive treatment to lactulose. It selectively targets gut bacteria responsible for ammonia production without being absorbed systemically.

Studies indicate that rifaximin, when combined with lactulose, reduces HE recurrence and improves quality of life in patients with cirrhosis (Bajaj et al. 2013). A randomized controlled trial showed that rifaximin reduced the risk of hospitalization for HE by nearly 50%, emphasizing its role as an important addition to lactulose therapy (Bass et al. 2010).

Emerging Therapies

While lactulose and rifaximin remain mainstays, newer therapies that directly target ammonia levels are under investigation. Ammonia scavengers such as ornithine phenylacetate and glycerol phenylbutyrate have shown promise in clinical trials. Ornithine phenylacetate works by facilitating the formation and excretion of phenylacetylglutamine, a compound that binds ammonia for renal excretion (Jalan et al. 2008). Clinical studies indicate that ornithine phenylacetate can effectively reduce blood ammonia levels in acute liver failure and HE, potentially reducing hospitalization rates (Vaquero et al. 2003). Glycerol phenylbutyrate, an oral ammonia scavenger approved for urea cycle disorders, has demonstrated effectiveness in lowering ammonia levels in cirrhotic patients. A study conducted with HE patients reported a significant reduction in both ammonia levels and HE episodes with glycerol phenylbutyrate, although further research is needed to fully establish its safety and efficacy profile in HE management (Ventura-Cots et al. 2021).

Given the central role of neuroinflammation in HE, anti-inflammatory therapies have attracted considerable interest. Albumin infusions have been studied for their potential anti-inflammatory and antioxidant effects. Albumin has been shown to improve outcomes in cirrhotic patients by reducing systemic inflammation and modulating immune response (Jalan and McPhail 2012). A randomized trial demonstrated that long-term albumin administration significantly decreased HE episodes and improved survival rates in cirrhotic patients, highlighting its potential as a supportive therapy for HE (Fernández et al. 2014). Additionally, statins, which are traditionally used for lipid-lowering, have demonstrated anti-inflammatory effects that could benefit HE patients. Studies suggest that statins reduce portal hypertension and have favorable effects on endothelial function, which may help preserve blood-brain barrier integrity and reduce neuroinflammation (Riggio et al. 2010). Preliminary research indicates that statins might reduce the incidence of HE episodes, but further studies are necessary to confirm these findings and establish the optimal dosing (Lee et al. 2012).

Oxidative stress and mitochondrial dysfunction play critical roles in HE pathogenesis, driving neuronal injury and cognitive decline. Antioxidant therapies aimed at countering oxidative damage have shown promise in preclinical and early clinical studies. N-acetylcysteine (NAC), a precursor to glutathione, is one such antioxidant being explored for its neuroprotective effects in HE. NAC has been shown to reduce oxidative stress markers and improve mental status in HE patients with acute liver failure, though evidence is still limited for chronic liver disease settings (Elsaid and Rustgi 2020). Another mitochondrial-targeted agent, L-carnitine, has shown benefits in improving cognitive function and fatigue in HE patients. L-carnitine aids mitochondrial function by facilitating fatty acid transport, which enhances energy production. A study found that L-carnitine supplementation led to a significant reduction in HE episodes and improved psychometric performance, suggesting that it may have a beneficial role in HE management (Hadjihambi et al. 2015).

The neurotransmitter imbalance in HE, particularly involving the GABAergic and glutamatergic systems, has spurred interest in therapies that modulate these pathways. Flumazenil, a benzodiazepine receptor antagonist, has been explored for its ability to counteract GABAergic tone in HE. Although flumazenil can temporarily improve mental status in some HE patients, its effects are short-lived, and it is generally not suitable for long-term management due to its limited efficacy and risk of side effects (Reverter et al. 2021). Recently, interest has also turned to astrocyte-targeted therapies that aim to reduce glutamine accumulation and thus prevent astrocyte swelling, which is associated with ammonia toxicity. Research is ongoing to develop agents that can safely modulate these neurotransmitter pathways without causing significant side effects (Bosoi and Rose 2013).
The gut-liver-brain axis is increasingly recognized as a significant factor in HE, and interventions targeting the gut microbiota have shown promise. Probiotics and synbiotics (combinations of probiotics and prebiotics) are being investigated for their potential to improve gut health, reduce ammonia production, and decrease systemic inflammation. Studies indicate that specific strains of probiotics can reduce ammonia levels and improve cognitive outcomes in HE patients, suggesting that microbiota modulation may offer an adjunctive approach to standard HE treatments (Horvath et al. 2016). One randomized trial demonstrated that probiotic administration was associated with reduced HE recurrence and improved psychometric performance, although more research is needed to standardize protocols for probiotic use in HE (Bajaj et al. 2008).

Conclusions

Hepatic encephalopathy represents a significant neuropsychiatric complication of liver disease, highlighting the intricate connections between liver disease and CNS dysfunction. HE pathogenesis involves multifaceted mechanisms, including ammonia toxicity, neuroinflammation, oxidative stress, neurotransmitter imbalance, and disruption of the gut-liver-brain axis. Recent advancements in understanding these mechanisms have guided the development of therapeutic approaches targeting specific aspects of HE, with a focus on reducing ammonia levels, managing neuroinflammation, protecting the blood-brain barrier, and modulating gut microbiota. While traditional treatments like lactulose and rifaximin

remain central to HE management, emerging therapies such as ammonia scavengers, anti-inflammatory agents, and probiotics offer promising complementary strategies. Further research and clinical trials are needed to validate these approaches, refine treatment protocols, and enhance patient outcomes, potentially transforming HE management and improving quality of life for those affected.

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All authors have read and agreed to the published version of the manuscript.

Conflict of Interest Statement:

The authors declare no conflicts of interest.

Funding Statement:

This study received no financial support.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

Acknowledgments:
None.

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