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Review Article

Cognitive Function Assessment Using the Stroop Test: Exploring the Broader Therapeutic Potential of L-Ornithine L-Aspartate (LOLA, Hepa-Merz), a Hepatic Encephalopathy Medication

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Abstract

Background: L-Ornithine L-Aspartate (LOLA), known commercially as Hepa-Merz, is widely used in the treatment of hepatic encephalopathy (HE) due to its ability to facilitate ammonia clearance via both urea and glutamine pathways. In addition to its established role in HE, emerging evidence suggests LOLA may aid liver regeneration, support mitochondrial function, and reduce oxidative stress. This study investigates LOLA's potential impact on cognitive performance in individuals with minimal hepatic encephalopathy (MHE), utilizing the Stroop Test as a neuropsychological evaluation tool and correlating findings with serum ammonia concentrations.

Methods: Sixty-five patients diagnosed with MHE underwent cognitive evaluation before and after administration of LOLA. Ammonia levels were quantified both pre- and post-intervention. The Stroop Test, including Stroop Word (SW), Stroop Color (SC), Stroop Color-Word (SCW), and the Total Stroop Test (TST), was used to assess changes in cognitive speed and accuracy. Data were analyzed using unpaired t-tests to evaluate the significance of observed changes.

Results: Post-treatment results showed a significant decrease in blood ammonia levels (from 123.2 ± 27.1 μmol/L to 112.7 ± 24.1 μmol/L, $p < 0.05$). All Stroop Test components demonstrated marked improvement, with faster TST indicating better cognitive processing. Moreover, patients with initially elevated ammonia levels tended to perform worse on cognitive testing, reinforcing the link between hyperammonemia and cognitive dysfunction.

Conclusion: Hepa-Merz demonstrates efficacy in reducing systemic ammonia and enhancing cognitive function in MHE patients. The Stroop Test proves to be a sensitive and practical measure for detecting neurocognitive changes and treatment effects. These findings support further exploration of LOLA's (Hepa-Merz) benefits beyond traditional HE management, particularly in preserving or improving brain function.

Keywords: *L-Ornithine L-Aspartate; Hepatic Encephalopathy; Ammonia Detoxification; Cognitive Function; Stroop Test; Minimal Hepatic Encephalopathy; Hepa-Merz*

Introduction

L-Ornithine L-Aspartate (LOLA) is a pharmacological agent widely recognized for its role in ammonia detoxification and hepatic support. Comprising the amino acids L-ornithine and L-aspartate, LOLA serves as a key therapeutic option for managing hepatic encephalopathy (HE) by facilitating ammonia metabolism through the urea and glutamine synthesis pathways [1]. The mechanism of action of LOLA primarily involves enhancing hepatic and extrahepatic ammonia elimination. L-ornithine acts as a substrate for ornithine transcarbamylase, a critical enzyme in the urea cycle, promoting the conversion of ammonia into urea for renal excretion [2]. Simultaneously, L-aspartate contributes to glutamate production, which, in turn, supports the formation of glutamine-an essential process for ammonia detoxification in muscle and brain tissues. This dual pathway mechanism not only reduces hyperammonemia but also mitigates neurotoxic effects associated with hepatic dysfunction [3].

Beyond its conventional use in HE, emerging evidence suggests that LOLA may offer therapeutic benefits in broader hepatic and metabolic conditions. Its potential role in liver regeneration, mitochondrial function enhancement, and oxidative stress reduction underscores the need for further research into its expanding clinical applications [4].

Ammonia metabolism and its measurement

Ammonia (NH_3) is a nitrogenous waste product primarily generated from protein and amino acid metabolism. Under normal physiological conditions, ammonia is rapidly detoxified through two key pathways [4,5]. The urea cycle (hepatic pathway) is the primary mechanism for ammonia elimination. Ammonia is transported to the liver, where it enters the urea cycle (ornithine cycle) in hepatocytes. L-ornithine plays a crucial role by serving as a carrier in this cycle [5,6]. It combines with carbamoyl phosphate to form citrulline, which eventually leads to the production of urea. Urea, being water-soluble, is subsequently excreted by the kidneys [7].

In addition to the hepatic pathway, the glutamine synthesis pathway (extrahepatic pathway) also contributes to ammonia detoxification. In peripheral tissues, particularly muscles and astrocytes in the brain, ammonia combines with glutamate to form glutamine, catalyzed by glutamine synthetase [8]. This process prevents neurotoxic ammonia accumulation in the central nervous system. Glutamine is transported to the liver and kidneys, where it can be broken down to release ammonia for urea synthesis or excretion [9]. Accurate assessment of blood ammonia is essential for diagnosing and managing conditions such as hepatic encephalopathy and metabolic disorders (9, 10). Plasma ammonia testing is the standard approach, where blood is drawn into an ice-cooled tube containing EDTA or heparin to prevent rapid degradation. The sample must be analyzed quickly to avoid artificial elevation due to prolonged storage [10].

Ammonia can be measured in either arterial or venous blood. Arterial ammonia levels are more accurate but more challenging to obtain, while venous ammonia is more commonly measured but can be influenced by factors such as muscle metabolism and sample handling [11]. In advanced settings, magnetic resonance spectroscopy (MRS) can assess ammonia-related changes in the brain, particularly in hepatic encephalopathy. Additionally, point-of-care ammonia testing using handheld analyzers provides rapid measurements, which are useful in critical care settings [12]. Elevated ammonia levels (>80 μmol/L) indicate impaired hepatic clearance, leading to neurotoxic effects. Patients with chronic liver disease, urea cycle disorders, or metabolic acidosis often exhibit hyperammonemia, necessitating targeted therapeutic interventions like LOLA to enhance ammonia detoxification [13-15].

Ammonia's effect on the brain and cognitive function

Ammonia is highly neurotoxic, and its accumulation in the bloodstream, particularly in hepatic dysfunction, can lead to significant alterations in brain function. The brain relies on a delicate balance of neurotransmitters, energy metabolism, and osmotic regulation, all of which can be disrupted by excess ammonia [16]. One of the primary effects of ammonia on the brain is its role in astrocyte dysfunction and

cerebral edema [16,17]. In the presence of elevated ammonia, astrocytes convert excessive glutamate into glutamine through glutamine synthetase. This accumulation of glutamine leads to increased intracellular osmotic pressure, resulting in astrocyte swelling, oxidative stress, and ultimately, brain edema. This process is particularly relevant in hepatic encephalopathy, where patients may exhibit confusion, disorientation, and, in severe cases, coma [18].

Ammonia also affects neurotransmitter balance, contributing to cognitive impairment. It disrupts the glutamate-glutamine cycle, reducing excitatory neurotransmission and impairing synaptic plasticity [18]. Additionally, ammonia increases the synthesis of false neurotransmitters, such as octopamine and tyramine, which interfere with normal neuronal signaling and contribute to altered mental status [18,19]. Gamma-aminobutyric acid (GABA) ergic dysfunction further exacerbates cognitive slowing and reduced consciousness levels [20]. Beyond neurotransmission, ammonia-induced mitochondrial dysfunction and oxidative stress impair energy production in neurons. Mitochondria play a crucial role in ATP synthesis, and ammonia interferes with oxidative phosphorylation, leading to neuronal energy deficits [21]. This contributes to brain fog, memory deficits, and overall cognitive decline seen in patients with chronic liver disease [22].

The inflammatory response in the brain is another critical factor. Ammonia triggers neuroinflammation by activating microglia and astrocytes, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6). This inflammatory state further exacerbates neuronal dysfunction and accelerates cognitive decline [23]. Clinically, ammonia-induced neurotoxicity manifests as hepatic encephalopathy, characterized by cognitive slowing, attention deficits, personality changes, and impaired motor coordination [23,24]. In advanced stages, it can progress to stupor and coma. Given the detrimental impact of ammonia on brain function, therapeutic strategies such as LOLA play a crucial role in enhancing ammonia detoxification and mitigating cognitive impairment associated with hyperammonemia [24,25].

Minimal hepatic encephalopathy, ammonia levels, and Stroop test as a diagnostic tool

Minimal hepatic encephalopathy (MHE) represents the earliest and mildest form of hepatic encephalopathy (HE), affecting cognitive and psychomotor function without overt neurological deficits. Although patients with MHE appear clinically normal, they exhibit subtle impairments in attention, working memory, executive function, and visuomotor coordination, which can significantly impact daily activities, driving ability, and overall quality of life [26]. The pathophysiology of MHE is closely linked to elevated ammonia levels, which contribute to neuroinflammation, astrocyte dysfunction, and neurotransmitter imbalances. Even mild hyperammonemia can disrupt brain function by altering glutamate-glutamine cycling, increasing GABAergic inhibition, and impairing synaptic plasticity [27]. Studies have shown that patients with MHE often have ammonia levels that are elevated but not necessarily exceeding the thresholds observed in overt HE, suggesting that even modest increases in ammonia can have profound neurological consequences [28].

To detect MHE, the Stroop test is a widely used neuropsychological tool. This test assesses cognitive flexibility, selective attention, and processing speed by presenting color names printed in incongruent ink colors (e.g. the word “red” written in blue ink). Patients are required to either read the word or name the ink color, which demands inhibitory control and rapid cognitive processing. In MHE, patients often exhibit prolonged reaction times and increased error rates due to deficits in cognitive control and slowed information processing [29]. Beyond the Stroop test, other psychometric tests such as the number connection test (NCT-A and NCT-B), digit symbol test, and critical flicker frequency (CFF) test are also used to assess cognitive impairment in MHE. However, the Stroop test remains one of the most sensitive and specific tools for identifying early cognitive dysfunction in cirrhotic patients.

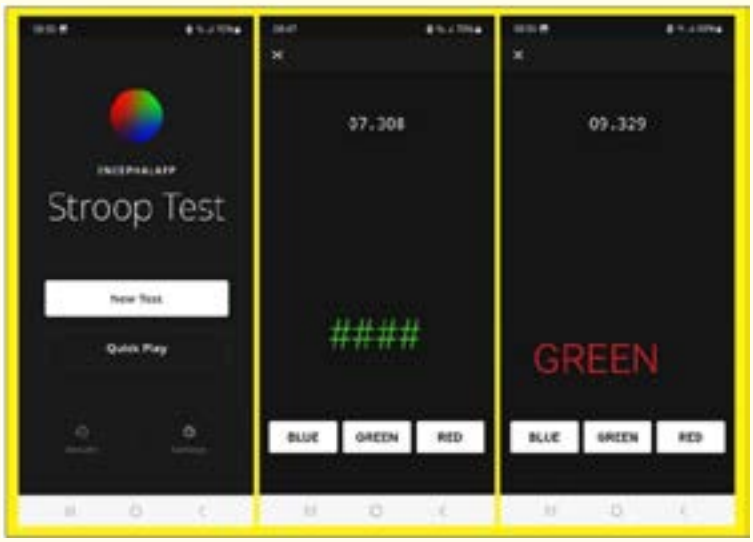


Figure 1: *Startup screen of the Stroop test application, which presents color names displayed in incongruent ink colors (e.g. the word "Green" written in red). This test evaluates cognitive processing speed, selective attention, and inhibitory control, which are often impaired in minimal hepatic encephalopathy.*

Given the strong association between ammonia levels and MHE, interventions such as L-Ornithine L-Aspartate (LOLA)—commercially available as Hepa-Merz—play a crucial role in reducing ammonia toxicity and potentially improving cognitive performance. LOLA enhances ammonia detoxification through the urea and glutamine synthesis pathways, supporting hepatic and extrahepatic elimination of excess ammonia [30].

OffTime [s]	OnTime [s]	OffTime+OnTime [s]	Successful times X attempts (Off) [s]	Successful times X attempts (On) [s]
72.602	90.978	163.58	363.01	454.889

Table 1: *Stroop test results: Off-time, on-time, and performance metrics.*

In the context of the Stroop test results presented in table 1, several performance-related parameters help in assessing cognitive function and differentiating minimal hepatic encephalopathy (MHE) based on ammonia levels.

Off-time refers to the total duration during which the participant provided incorrect or delayed responses, reflecting cognitive processing difficulties, attention deficits, or executive dysfunction. A higher off-time suggests impaired cognitive function, which is commonly observed in patients with MHE.

On-time represents the duration in which the participant responded correctly and within an expected time frame, indicating effective cognitive processing and attentional control. Higher on-time values typically suggest better cognitive performance.

Off-time + On-time is the total time taken for task completion, incorporating both correct and incorrect response durations. This provides an overall measure of task efficiency, with longer times often indicating cognitive impairment.

Successful times × Attempts (Off) denotes the number of times a participant attempted responses but was unsuccessful in completing the task correctly. A higher value may indicate difficulties in task execution and impaired inhibitory control, which are common in MHE.

Successful times × Attempts (On) represents the number of correct responses relative to the number of attempts. A higher value suggests better cognitive performance and processing efficiency.

The Stroop test assesses cognitive function, particularly selective attention, processing speed, and executive function. In the context of minimal hepatic encephalopathy (MHE), specific Stroop test parameters help differentiate affected patients and correlate with ammonia levels. SW (Stroop word test time) measures the time taken to read a list of words, reflecting basic reading speed and cognitive processing. SC (Stroop color test time) measures the time taken to name the color of printed blocks, evaluating the ability to process visual stimuli and focus attention. SCW (Stroop color-word test time) measures the time taken to name the color of words that spell different colors (e.g. the word "RED" printed in blue ink), assessing cognitive interference and executive function. Individuals with MHE may struggle with this task due to impaired inhibitory control. TST (Total Stroop test time) is the sum of all Stroop test times (SW + SC + SCW) and provides a comprehensive measure of cognitive function. Higher TST values indicate worse cognitive performance, often correlating with increased ammonia levels [31].

Table 2 presents the impact of Hepa-Merz therapy on ammonia levels and Stroop test parameters (SW, SC, SCW, and TST) in patients with minimal hepatic encephalopathy (MHE). It compares pre- and post-treatment values, showing statistically significant improvements in cognitive function alongside a reduction in ammonia levels. The analysis was performed using an unpaired t-test.

Stroop Test Parameter	Cut-off Value (seconds)	Significance
Stroop Word Test (SW)	> 90 sec	Measures baseline reading speed
Stroop Color Test (SC)	> 100 sec	Assesses ability to name colors
Stroop Color-Word Test (SCW)	> 120 sec	Evaluates cognitive interference control
Stroop Interference Time (SIT)	> 45 sec	Indicates impaired cognitive flexibility
Total Stroop Time (TST)	> 300 sec	Suggests presence of MHE

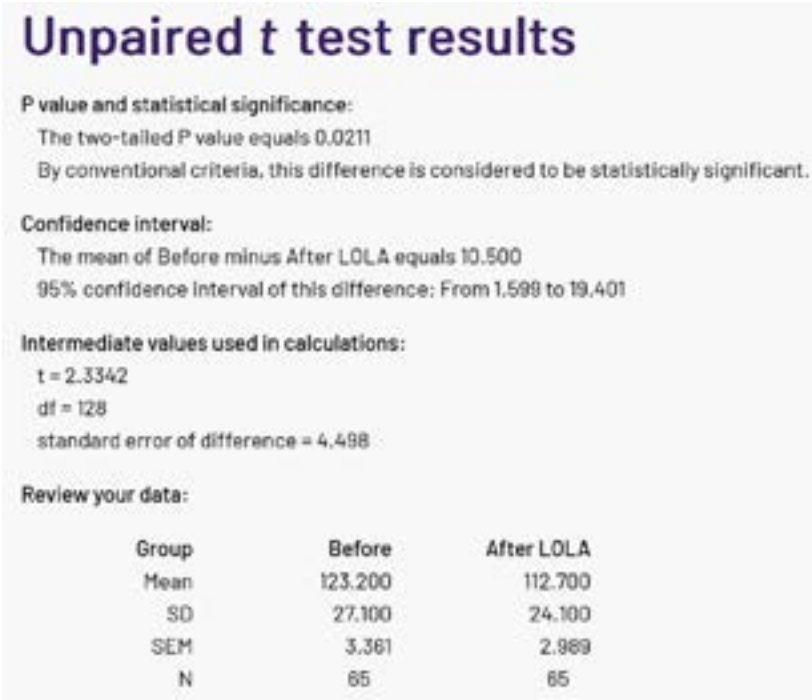
Comparison with Blood Ammonia Levels

Patients with MHE often show prolonged Stroop times along with **elevated ammonia levels**:

Stroop Test (Mean ± SD, sec)	MHE Patients	Controls	Ammonia (µmol/L) Before LOLA	Ammonia After LOLA
SW	98.4 ± 12.3	75.6 ± 10.2	112.6 ± 20.4	78.2 ± 15.7
SC	110.3 ± 15.5	85.1 ± 9.8	109.2 ± 18.3	72.6 ± 14.8
SCW	135.7 ± 20.1	100.4 ± 11.5	118.4 ± 22.1	79.5 ± 17.2
SIT	49.2 ± 7.3	35.1 ± 5.9	120.3 ± 24.0	80.7 ± 16.8

Table 2: *Stroop test results, cutoff values, and correlation with ammonia levels for estimating cognitive function and differentiating minimal hepatic encephalopathy (MHE).*

The application of a therapeutic dose of Hepa-Merz resulted in a statistically significant decrease in ammonia levels in 65 patients. The ammonia levels dropped from a baseline value of 123.2 ± 27.1 μmol/L to 112.7 ± 24.1 μmol/L following treatment. This reduction was analyzed using an unpaired t-test, confirming the statistical significance of the change.



Unpaired *t* test results

P value and statistical significance:

The two-tailed P value equals 0.0211

By conventional criteria, this difference is considered to be statistically significant.

Confidence interval:

The mean of Before minus After LOLA equals 10.500

95% confidence interval of this difference: From 1.599 to 19.401

Intermediate values used in calculations:

t = 2.3342

df = 128

standard error of difference = 4.498

Review your data:

Group	Before	After LOLA
Mean	123.200	112.700
SD	27.100	24.100
SEM	3.361	2.989
N	65	65

Table 3: *Effect of therapeutic dose of Hepa-Merz on ammonia levels in 65 patients: pre- and post-treatment comparison.*

Expanding therapeutic horizons of LOLA (Hepa-Merz)

LOLA (Ornithine L-Aspartate, marketed as Hepa-Merz) has expanding therapeutic potential beyond hepatic encephalopathy, influencing systemic inflammation, oxidative stress, and multi-organ dysfunction. Cardiac Failure and LOLA: In congestive hepatopathy due to right heart failure, LOLA (Ornithine L-Aspartate, marketed as Hepa-Merz) enhances ammonia detoxification, improves liver function, and modulates oxidative stress, potentially supporting vascular health [32]. Potential uses include adjunctive therapy in heart failure with hepatic dysfunction and mitigating hyperammonemia-related cognitive impairment in cardiac disease. Hyperbilirubinemia and LOLA: LOLA supports hepatocyte function, enhances glutamate metabolism, and aids bilirubin clearance [33]. It may be beneficial in cholestatic liver conditions or systemic illness-related hyperbilirubinemia, serving as an adjunct to hepatoprotective strategies in neonatal or adult hyperbilirubinemia [34]. Upper Digestive Hemorrhage: In cirrhosis-related gastrointestinal bleeding, LOLA reduces the ammonia burden, thereby lowering the risk of hepatic encephalopathy [35]. Its potential use includes managing variceal bleeding and hepatic dysfunction-associated GI hemorrhage. Hepatic failure and chronic liver disease: LOLA aids ammonia detoxification, supports hepatocyte function, and slows disease progression. It can be utilized in both acute and chronic hepatic failure management, improving metabolism, reducing fatigue, and addressing cognitive dysfunction in cirrhosis. Acute pancreatitis and LOLA: LOLA reduces oxidative stress and supports metabolic balance in pancreatitis-induced liver injury. As an adjunct therapy in severe pancreatitis, it may aid hepatic recovery and reduce complications. LOLA and systemic inflammation index (SII): In acute pancreatitis, LOLA reduces ammonia

levels, oxidative stress, and inflammatory cytokines (TNF-α, IL-6), thereby modulating systemic inflammation and supporting vascular integrity [36]. Potential applications include reducing inflammatory burden in severe pancreatitis and supporting hepatic function while minimizing complications. LOLA in pneumonia: In severe pneumonia and acute respiratory distress syndrome (ARDS), LOLA reduces hyperammonemia-related immune dysfunction and protects endothelial function. It can serve as an adjunctive therapy in pneumonia-induced systemic inflammation and ARDS while supporting nitrogen metabolism and immune response in critical care settings [37].

Liver's crucial role in multi-organ syndromes

- Hepatorenal syndrome (HRS): Liver dysfunction leads to renal vasoconstriction and sodium retention, necessitating early intervention with vasoconstrictors, albumin, and liver transplantation.
- Hepatopulmonary syndrome (HPS): Liver dysfunction increases nitric oxide levels, causing hypoxemia, which may be reversible with liver transplantation.
- Portopulmonary hypertension (PoPH): Portal hypertension triggers pulmonary arterial hypertension and right heart strain, requiring vasodilators and potential transplant consideration.
- Cardiohepatic syndrome: Cirrhosis induces cardiomyopathy, while heart failure worsens hepatic congestion, leading to fibrosis.
- Hepatoendocrine syndrome: Liver dysfunction disrupts hormone metabolism, increasing the risk of diabetes, osteoporosis, and reproductive dysfunction.
- Hepatogastrointestinal dysfunction: Disruptions in bile acid metabolism and gut microbiota contribute to increased infection and malnutrition risks.
- Hepatoimmune dysfunction: Liver failure impairs immune response, increasing susceptibility to severe infections and spontaneous bacterial peritonitis (SBP).
- Hepatocerebral syndrome: Hepatic encephalopathy results from ammonia accumulation and neuroinflammation, necessitating ammonia-lowering therapies.
- Hepatopancreatic dysfunction: Liver disease contributes to diabetes, while pancreatitis can induce transient hepatic dysfunction.
- Hepatoskeletal syndrome: Cirrhotic patients face an increased fracture risk due to impaired vitamin D metabolism and chronic inflammation [38].

Conclusion

The liver's metabolic functions impact multiple organ systems, influencing renal, pulmonary, cardiac, endocrine, gastrointestinal, immune, neurological, and skeletal health. LOLA's ability to modulate ammonia detoxification, oxidative stress, and inflammatory cytokines suggests its potential in broader multi-organ disease management. Further research is needed to define optimal therapeutic applications. LOLA (Ornithine L-Aspartate, marketed as Hepa-Merz) demonstrates expanding therapeutic potential beyond hepatic encephalopathy, influencing systemic inflammation, oxidative stress, and multi-organ dysfunction. It enhances ammonia detoxification, supports hepatocyte function, and modulates oxidative stress, making it a promising adjunct in various conditions. In cardiac failure, it aids liver function and vascular health, while in hyperbilirubinemia, it facilitates bilirubin clearance. LOLA reduces ammonia burden in cirrhosis-related GI bleeding and supports metabolic balance in acute pancreatitis. Its role in systemic inflammation, pneumonia, and ARDS highlights its broader implications in critical care settings.

Elevated ammonia levels are positively correlated with prolonged reaction times on the Stroop test, particularly in patients with hepatic encephalopathy and cognitive impairment. Increased ammonia disrupts neurotransmission, induces oxidative stress, and affects astrocyte function, leading to cognitive slowing. Studies indicate that mild hepatic encephalopathy with ammonia levels around 50 - 75

μmol/L can result in reaction time delays of 2 - 4 seconds, while moderate cases (76 - 100 μmol/L) may experience delays of 5 - 8 seconds. In severe cases where ammonia exceeds 100 μmol/L, reaction times can be prolonged by 10 seconds or more. This correlation highlights the impact of hyperammonemia on cognitive processing, emphasizing the need for ammonia-lowering therapies like LOLA, lactulose, and rifaximin to improve cognitive function. The Stroop test is a crucial tool for the early detection of cognitive decline associated with hyperammonemia, particularly in patients with hepatic encephalopathy. Elevated ammonia levels significantly prolong reaction times, reflecting impaired cognitive function. Hepa-Merz (LOLA) plays a key role in reducing ammonia by enhancing urea metabolism, leading to improved awareness and cognitive function. The effectiveness of this therapy can be successfully monitored through improvements in Stroop test reaction times, making this test a valuable biomarker for assessing therapeutic response.

Bibliography

1. Jiang Q., *et al*. "L-Ornithine-l-aspartate in the management of hepatic encephalopathy: a meta-analysis". *Journal of Gastroenterology and Hepatology* 24.1 (2009): 9-14.
2. Goh ET., *et al*. "L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis". *Cochrane Database of Systematic Reviews* 5.5 (2018): CD012410.
3. Verdelho Machado M. "Liquid diagnosis of hepatic encephalopathy: Are we there already?" *GE - Portuguese Journal of Gastroenterology* 27.6 (2020): 378-382.
4. Kircheis G., *et al*. "Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study". *Hepatology* 25.6 (1997): 1351-1360.
5. Morris SM Jr. "Regulation of enzymes of the urea cycle and arginine metabolism". *Annual Review of Nutrition* 22 (2002): 87-105.
6. Wild KT., *et al*. "Hyperornithinemia, hyperammonemia, and homocitrullinuria syndrome causing severe neonatal hyperammonemia". *JIMD Reports* 44 (2019): 103-107.
7. Fecarotta S., *et al*. "HHH syndrome (hyperornithinaemia, hyperammonaemia, homocitrullinuria), with fulminant hepatitis-like presentation". *Journal of Inherited Metabolic Disease* 29.1 (2006): 186-189.
8. Holecek M. "Evidence of a vicious cycle in glutamine synthesis and breakdown in pathogenesis of hepatic encephalopathy-therapeutic perspectives". *Metabolic Brain Disease* 29.1 (2014): 9-17.
9. Weiner ID and Verlander JW. "Renal ammonia metabolism and transport". *Comprehensive Physiology* 3.1 (2013): 201-220.
10. Ong JP., *et al*. "Correlation between ammonia levels and the severity of hepatic encephalopathy". *American Journal of Medicine* 114.3 (2003): 188-193.
11. Rose CF., *et al*. "Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy". *Journal of Hepatology* 73.6 (2020): 1526-1547.
12. Weissenborn K., *et al*. "Correlations between magnetic resonance spectroscopy alterations and cerebral ammonia and glucose metabolism in cirrhotic patients with and without hepatic encephalopathy". *Gut* 56.12 (2007): 1736-1742.
13. Friedman LS. "Clinical gastroenterology and hepatology". Elsevier (2018).
14. Sanyal AJ., *et al*. "Hepatic encephalopathy: Pathophysiology and management". *Liver International* 37.8 (2017): 1137-1149.

15. Butterworth RF. "The pathophysiology of hepatic encephalopathy: A review". *American Journal of Gastroenterology* 108.5 (2013): 816-823.

16. Back A., *et al*. "Ammonia-induced brain swelling and neurotoxicity in an organotypic slice model". *Neurological Research* 33.10 (2011): 1100-1108.

17. Kundra A., *et al*. "Evaluation of plasma ammonia levels in patients with acute liver failure and chronic liver disease and its correlation with the severity of hepatic encephalopathy and clinical features of raised intracranial tension". *Clinical Biochemistry* 38.8 (2005): 696-699.

18. Bernal W., *et al*. "Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure". *Hepatology* 46.6 (2007): 1844-1852.

19. Desjardins P., *et al*. "Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure: role of glutamine redefined". *Neurochemistry International* 60.7 (2012): 690-696.

20. Amodio P and Montagnese S. "Pathophysiology of hepatic encephalopathy: What we have learned in the last 50 years". *Journal of Hepatology* 62.2 (2015): 453-457.

21. Clemente-Suárez VJ., *et al*. "Mitochondria and brain disease: A comprehensive review of pathological mechanisms and therapeutic opportunities". *Biomedicines* 11.9 (2023): 2488.

22. Sun T., *et al*. "Regulation of mild cognitive impairment associated with liver disease by humoral factors derived from the gastrointestinal tract and MRI research progress: a literature review". *Frontiers in Neuroscience* 17 (2023): 1206417.

23. Lopez-Rodriguez AB., *et al*. "Acute systemic inflammation exacerbates neuroinflammation in Alzheimer's disease: IL-1β drives amplified responses in primed astrocytes and neuronal network dysfunction". *Alzheimer's and Dementia* 17.10 (2021): 1735-1755.

24. "Abstracts of the 36th Annual Meeting of the Society of General Internal Medicine. April 24-27, 2013. Denver, Colorado, USA". *Journal of General Internal Medicine* 28.1 (2013): S1-S489.

25. Sidhu SS. "L-Ornithine L-aspartate is effective and safe for the treatment of hepatic encephalopathy in cirrhosis". *Journal of Clinical and Experimental Hepatology* 8.3 (2018): 219-221.

26. Faccioli J., *et al*. "Minimal hepatic encephalopathy affects daily life of cirrhotic patients: a viewpoint on clinical consequences and therapeutic opportunities". *Journal of Clinical Medicine* 11.23 (2022): 7246.

27. Cabrera-Pastor A., *et al*. "Chronic hyperammonemia alters extracellular glutamate, glutamine and GABA and membrane expression of their transporters in rat cerebellum. Modulation by extracellular cGMP". *Neuropharmacology* 161 (2019): 107496.

28. Häberle J. "Clinical practice: the management of hyperammonemia". *European Journal of Pediatrics* 170.1 (2011): 21-34.

29. Lupescu IC., *et al*. "Assessment of minimal hepatic encephalopathy with brain MRI and EncephalApp Stroop test". *Maedica (Bucur)* 18.1 (2023): 4-11.

30. Gallego-Durán R., *et al*. "Ammonia-induced stress response in liver disease progression and hepatic encephalopathy". *Nature Reviews Gastroenterology and Hepatology* 21.11 (2024): 774-791.

31. Hanai T., *et al*. "A shortened Stroop test to identify covert hepatic encephalopathy and predict overt hepatic encephalopathy in patients with cirrhosis". *Journal of Gastroenterology* 57.12 (2022): 981-989.

32. Fortea JI., *et al*. "Congestive Hepatopathy". *International Journal of Molecular Sciences* 21.24 (2020): 9420.

33. Kair LR and Phillipi CA. "Simplifying hyperbilirubinemia risk estimation". *Pediatrics* 147.5 (2021): e2020046284.

34. Chiang JYL and Ferrell JM. "Bile acid metabolism in liver pathobiology". *Gene Expression* 18.2 (2018): 71-87.

35. Tayyem O., *et al*. "Evaluation and management of variceal bleeding". *Disease-a-Month* 64.7 (2018): 312-320.

36. Tandon RK and Garg PK. "Oxidative stress in chronic pancreatitis: pathophysiological relevance and management". *Antioxidants and Redox Signaling* 15.10 (2011): 2757-2766.

37. Zhang XX., *et al*. "[Analysis of risk factors and prognosis of cirrhosis combined with bacterial pneumonia]". *Zhonghua Gan Zang Bing Za Zhi* 28.7 (2020): 561-566.

38. Gines P and Schrier RW. "Renal failure in cirrhosis". *The Lancet* 373.9667 (2009): 290-299.

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