Altered Level of Consciousness in Metabolic Disease: An Emphasis on the Pathomechanism of Hepatic Encephalopathy

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Abstract.
The present study reports the first comprehensive study on the freshwater macroinvertebrates and its habitat preferences in Bilah River, the largest riverin the Northern Sumatra. The riverside is characterized by the presence of anthropogenic and industrial activities which may alter the macroinvertebrate assemblage and biodiversity. Five months of investigation on 10 sampling stations from December 2016 to October 2017 was conducted based on the river flow in Bilah River. Principal component analysis indicated a decrease in trophic status from upstream to downstream of the river. A total of 27 taxa were recorded, with the most abundant group were members of Odonata, Gastropoda, and Decapoda. The highest density of macroinvertebrate was observed from station 1 (160 ind m-2), while the lowest density was observed from station 9 (38.64 ind m^{-2}). Based on species distribution and similarity, two groups of habitats may be distinctively recognized based on the Bray-curtis similarity coefficient. Group 1 consisted of station 1, 2, 3 and 4 while group 2 consisted of station 5, 6, 7, 8, 9, and 10. Based on the diversity indices as ecological parameters, the habitat condition in Bilah River is categorized from low to moderately polluted. Spatial patterns in both environmental conditions affecting the macroinvertebrate assemblage was observed using canonical correspondence analysis (CCA) revealed the preferences from each macroinvertebrate species towards environmental conditions.
Keywords: *Altered level of consciousness, encephalopathy, metabolic disease and pathophysiolog.*

I. INTRODUCTION

Altered level of consciousness (ALOC) is a condition of reduced alertness or attention due to low awareness of the environment. This condition can be classified into decrease of arousal, the content of consciousness, or both [1], [2]. Change of consciousness is one of the major problem in emergency department and contributes around 5% to 40% of the emergency department patient [3]. ALOC can be caused by traumatic such as brain injury, and non-traumatic such as metabolic diseases [4].

Metabolic encephalopathy is a temporary or permanent diffuse cerebral dysfunction affecting the hemispheres, brainstem, and reticular activating system without primary structural dysfunction and typically manifested as disorders of mental functioning [5]. Metabolic encephalopathy are often caused by hypoxia, electrolyte disorder, or systemic organ failure including hepatic, renal, or pancreatic failure [6]. A study in Netherlands reported that 72% of decreased level of consciousness cases are due to metabolic causes [7]. Hepatic encephalopathy (HE) is one of the main causes, contributing 45-80% of cases in patients with cirrhosis [5].

HE is defined as brain dysfunction caused by liver disease and/or portal-systemic shunting, characterized as neuropsychiatric abnormalities ranging from subtle cognitive changes to coma. HE is one of the most common complications of cirrhosis leading to higher mortality rates. The pathogenesis of HE involves neurotoxic material which is ammonia, stimulating inflammatory response from astrocytes and lead to swelling and cerebral edema [8]. HE can also occurs without underlying of liver dysfunction, such as extrahepatic portal vein obstruction with shunting [9], [10].

HE, as one of the most frequent causes for encephalopathy is crucial for clinicians faced with patients presenting with ALOC. This narrative review aims to provide a practical clinical approach to ALOC in

metabolic diseases, emphasizing on hepatic causes, to assist clinicians in early recognition, targeted evaluation, and optimal management of this complex condition.

II. METHODS

This study is a narrative literature review that provides overview about altered consciousness causes by metabolic diseases especially hepatic causes. We used PubMed, Google Scholar, ScienceDirect to search for related publications from the last 10 years. The search terms were the following: Altered level of consciousness OR altered consciousness OR decreased consciousness OR altered mental status OR encephalopathy AND metabolic disease AND hepatic failure OR liver failure OR liver disease. The authors then reviewed and discussed each publication that met the criteria.

III. RESULT AND DISCUSSION

Initial Approach for Altered Level of Consciousness

Patients presenting with ALOC need to be assessed thoroughly with four components of care including history, examination, investigation and management at the same time. Evaluation for airway, breathing, circulation, disability, and exposure (ABCDE) should be done for every patient presents with ALOC. Obtaining patient's medical history from relatives familiar with the patient recent condition or other sources such as medical history can provide valuable information to determine the next step to manage the patient [4], [11]. Level of consciousness should be objectively measured. Instruments that can be used to measured consciousness are Glasgow Coma Scale (GCS) and AVPU (Alert, responsive to voice, responsive to pain, unresponsive) [4], [12], [13].

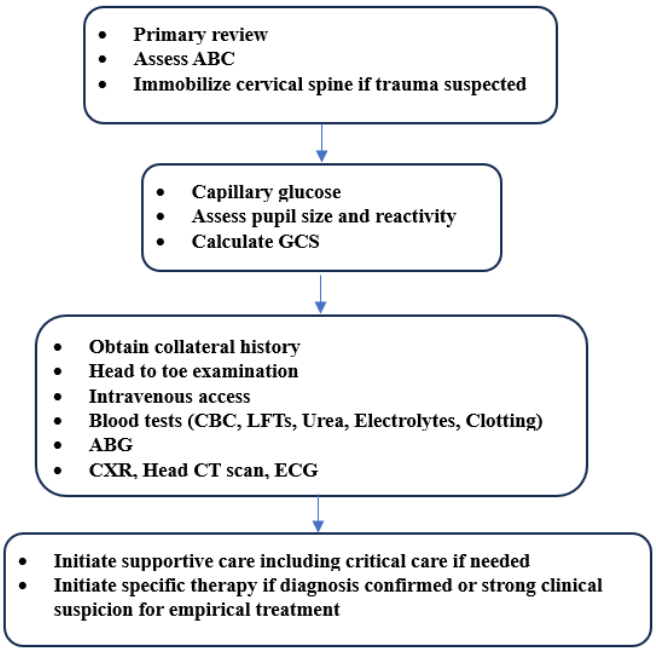

Fig. 1. Systematic Approaches to Altered Level of Consciousness Patient [4]

ABC. Airway, Breathing, Circulation; GCS. Glasgow Coma Scale; CBC. Complete Blood Count; LFTs. Liver Function Tests; ABG. Arterial Blood Gasses; CXR. Chest X Ray; ECG. Electrocardiogram

Encephalopathy Caused by Metabolic Disorders

Some studies suggested metabolic encephalopathy is more a symptom than a disease, including pathological conditions and usually manifested by altered mental disorder [5]. Metabolic encephalopathy is not caused by primary structural abnormalities, but from systemic disease. Etiologies of metabolic encephalopathy can be caused due to peripheral organ dysfunction including sepsis, HE, uremic encephalopathy, pancreatic failure, thyroid, acute pulmonary disease or post-transplant reaction. The other classification is due to lack of glucose, oxygen, or other metabolic factors including electrolyte disorders,

vitamin deficiencies, hypoxia and glucose disorders [14], [15], [16]. The pathophysiology of encephalopathy involve metabolic disorders leading to impaired neurons and astrocytes function. In more severe cases, metabolic disorders can also affect the ascending reticular activating system (ARAS) in the brain hence the reduced arousal and altered consciousness [17]. Organ failure can also cause neuronal dysfunction indirectly, through insufficient substrates such as oxygen, glucose, or accumulation of toxic metabolites [15]. In sepsis associated encephalopathy, systemic inflammation activates cerebral endothelial cells and causes dysfunction of the blood brain barrier allowing cytokines and chemokines to enter brain parenchyma and causing damage in the neocortex and hippocampus [5], [18], [19].

Pathophysiology of Hepatic Encephalopathy

The complete pathophysiology and mechanisms of HE are still not fully understood, one of the widely accepted concepts is neurologic and cognitive impairment promotes by liver disease are caused by blood-derived factors disrupting the permeability of blood brain barrier (BBB) [10], [20].

1. Ammonia

Increased level of serum ammonia is one of the main metabolic factors in the development of HE [21]. Ammonia is a small nitrogenous metabolite originating from the degradation of proteins and amino acids. The intestine and kidneys are the two primary sources of ammonia. Within the intestine, ammonia is produced through the breakdown of urea derived from dietary protein, and degradation of amino acid in the enterocytes. While in the kidneys, ammonia is produced from the glutamine in proximal tubular cells [22]. The liver has urea cycle regulating ammonia levels in the systemic circulation. L-ornithine L-aspartate (LOLA) acts as a substrate for the urea cycle, helping to reduce ammonia levels by increasing the activity of glutamine synthetase and urea cycle enzymes. However, in hepatic failure conditions, this process is disrupted and elevating ammonia levels in systemic circulation [23], [24]. Increased ammonia levels in blood can cross the BBB. Ammonia in the brain will be converted into glutamine mediated by glutamine synthetase in astrocytes. Glutamine accumulation in astrocytes can cause swelling and cytotoxic edema leading to encephalopathy [10], [21].

2. Inflammation

Systemic inflammation plays an important role in the development of HE. The inflammatory response is induced by infective pathogens as seen in infection, or damaged cells caused by ischemia, toxins, or injuries. This response leads to activation of pro-inflammatory cytokines such as TNF-alpha, interleukin (IL)-1, IL-1β and IL-6. This cytokine storm results in tissue injury from reactive oxygen species and complement activation [22], [25]. Pro-inflammatory cytokines as mentioned before, are released into the blood circulation and may cross the BBB causing neuroinflammation and oxidative stress. Hyperammonia and neuroinflammation have a synergistic effect developing HE. Elevated ammonia level can cause oxidative and nitrosative stress (ONS), cellular senescence, and activate glial cells which leads to neuroinflammation. Increasing evidences have highlighted the role of inflammation, whether triggered by infection or as a response of hepatic failure as a key to determine the severity and clinical outcomes of HE. Liver failure can also induce peripheral inflammation and increases BBB permeability causing neuroinflammation [25], [26], [27].

3. Gut Microbiomes

Dysruptions in the gut microbiomes shows major contribution to the development of HE. The components of the gut microbiomes including bacteria, fungi and viruses interact with one another, with the host, and with dietary components and medications. Certain taxa within the phylom *Proteobacteria* including *E. coli* and *Klebsiella pneumoniae* are considered harmful since they generate endotoxins. In contrast, several gram-positive Clostridial families such as Lachnospiraceae and Ruminococcaceae are thought to be beneficial due to their capacity to produce short-chain fatty acids and have a role in converting bile acids. Some studies showed that reduced bile acid synthesis in advanced liver disease causes overgrowth of pathogenic, urease-producing bacteria such as Enteriobacteriaceae, while reducing commensal bacteria such as Lanchnospiraceae [10], [22].

In cirrhosis patient, defective small intestinal motility, decreased gastric acid, and impaired intestinal mucosal immunity contribute to small intestinal bacterial overgrowth (SIBO). When combined with a

decrease in bile acids production, these conditions cause pathological changes in microbiomes composition, leading to marked reduction in microbial diversity, a decline in autochthonous non-pathogenic bacteria such as Bacteroidetes, Ruminococcus, Roseburia, Veillonellaceae, and Lachnospiraceae and expansion in potentially pathogenic species such as Fusobacteria, Proteobacteria, Enterococcaceae, and Streptococcaceae. The reduction in bacteria responsible for producing short-chain fatty acids and converting bile acids further aggravates gut dysbiosis and impairs intestinal barrier integrity. Dysruption of intestinal barrier promotes bacterial translocation and allows bacterial components endotoxins including lipopolysaccharides, flagellin, peptidoglycan, and microbial nucleic acids to enter the systemic circulation leading to worsened liver injury and systemic inflammation, ultimately contributing to BBB dysfunction and neuroinflammation [21], [28].

4. Malnutrition and Sarcopenia

Malnutrition frequently occurs in CLD. The etiologies include inadequate nutritional intake, increased energy expenditure, maldigestion and malabsorption. As metabolic rate increases, the body begins breaking down muscle proteins, worsened by depletion of glycogen stores and impairment in glycogenolysis. Elevated serum ammonia levels can also further damage muscle tissue by inhibiting protein synthesis leading to a harmful cycle. Sarcopenia is defined by a reduction in muscle size and function leading to diminished physical capacity. Muscle wasting also increases the likelihood of HE due to muscle tissue contains glutamine synthetase and have a crucial role in ammonia detoxification. Muscle breakdown promotes glutamine release, which can generate ammonia via glutaminase causing increased ammonia level [10], [23], [29].

5. Electrolyte Imbalance

Hyponatremia is among the most frequent electrolyte disorders in patients with cirrhosis. Serum sodium levels < 135 mmol/L are linked to a higher likelihood of complications including ascites, renal failure, sepsis, HE and increased mortality. Hyponatremia in cirrhosis develops through several mechanisms such as splanchnic vasodilatation and elevated antidiuretic hormone (ADH) secretion. Cirrhotic patients experience a pathological depletion of brain organic osmolytes, which physiologically helps in osmotic regulation during hyponatremia. As a result, this regulation becomes exaggerated, contributing to the development of HE and neurological manifestations. Some study reported that every 1 mmol/L drop in serum sodium, will increase the risk of HE by 8% [30].

6. Manganese

Manganese (Mn) is one of the crucial elements involved in multiple physiological processes, however in advanced liver disease, it has been associated with significant neurotoxin effect. In physiologic condition, excess Mn is eliminated through biliary excretion. Patients with CLD lead to increased Mn levels and subsequently accumulate within the central nervous system particularly the basal ganglia. Increased level of Mn induces cellular impairments, especially astrocytes because of their high affinity to Mn. Within astrocytes, Mn localizes to mitochondria, disrupting oxidative phosphorylation and cellular stress leading to impaired astrocyte-neuronal interactions. Clinically, Mn accumulation manifests as psychomotor and neuropsychiatric impairment [10], [22].

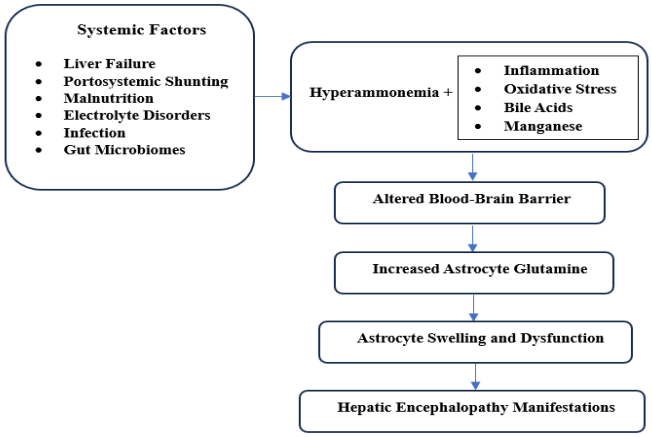

Fig. 2. Pathomechanism of Hepatic Encephalopathy.

IV. CONCLUSION

Altered level of consciousness in metabolic diseases represents a broad clinical spectrum requiring systematic assessment to make sure of the diagnosis and management. Hepatic encephalopathy is one of the most common causes of metabolic encephalopathy due to its prevalence, severity, and pathophysiology mechanism. Current evidence highlights the complex interactions between hyperammonemia, systemic inflammation, gut microbiomes dysbiosis, electrolyte disorders, malnutrition, and manganese in causing neuroinflammation and neurocognitive disturbances. Understanding these mechanisms is essential for early recognition and optimizing patient outcomes.

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REFERENCES

[1] H. A. Ali and M. F. Y. Mohamud, "Epidemiology, Risk Factors and Etiology of Altered Level of Consciousness Among Patients Attending the Emergency Department at a Tertiary Hospital in Mogadishu, Somalia," ***Int. J. Gen. Med.***, vol. 15, pp. 5297–5306, May 2022, doi: 10.2147/IJGM.S364202.

[2] L. Patti and M. Gupta, "Change in Mental Status," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2025. Accessed: Nov. 22, 2025. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK441973/

[3] S. Jung, J. C. Jeon, C.-G. Jung, Y. W. Cho, and K. T. Kim, "The etiologies of altered level of consciousness in the emergency department," ***J. Neurocritical Care***, vol. 13, no. 2, pp. 86–91, Sep. 2020, doi: 10.18700/jnc.200010.

[4] T. Cooksley, S. Rose, and M. Holland, "A systematic approach to the unconscious patient," *Clin. Med.*, vol. 18, no. 1, pp. 88–92, Feb. 2018, doi: 10.7861/clinmedicine.18-1-88.

[5] I. I. Berisavac *et al.*, "How to recognize and treat metabolic encephalopathy in Neurology intensive care unit," *Neurol. India*, vol. 65, no. 1, p. 123, Feb. 2017, doi: 10.4103/0028-3886.198192.

[6] M. Tomkins, R. McCormack, K. O'Connell, A. Agha, and Á. Merwick, "Metabolic encephalopathy secondary to diabetic ketoacidosis: a case report," *BMC Endocr. Disord.*, vol. 19, p. 71, Jul. 2019, doi: 10.1186/s12902-019-0398-8.

[7] M. D. Sharifi, G. Latifian Esafahani, M. Foroughian, and E. Vafadar Moradi, "The Etiology of Non-traumatic Loss of Consciousness in Patients Admitted to the Emergency Department," *Arch. Neurosci.*, vol. 11, no. 4, Aug. 2024, doi: 10.5812/ans-146116.

[8] A. Potnis, S. VanMeter, and J. Stange, "Prevalence of Hepatic Encephalopathy from a Commercial Medical Claims Database in the United States," ***Int. J. Hepatol.***, vol. 2021, no. 1, p. 8542179, 2021, doi: 10.1155/2021/8542179.

[9] P. Mandiga, S. Kommu, and P. C. Bollu, "Hepatic Encephalopathy," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2025. Accessed: Nov. 23, 2025. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK430869/

[10] C. F. Rose *et al.*, "Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy," *J. Hepatol.*, vol. 73, no. 6, pp. 1526–1547, Dec. 2020, doi: 10.1016/j.jhep.2020.07.013.

[11] Z. A. Bauer, O. De Jesus, and J. L. Bunin, "Unconscious Patient," in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2025. Accessed: Nov. 25, 2025. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK538529/

[12] M. Braun, W. U. Schmidt, M. Möckel, M. Römer, C. J. Ploner, and T. Lindner, "Coma of unknown origin in the emergency department: implementation of an in-house management routine," ***Scand. J. Trauma Resusc. Emerg. Med.***, vol. 24, p. 61, Apr. 2016, doi: 10.1186/s13049-016-0250-3.

[13] T. Cooksley and M. Holland, "The management of coma," *Medicine (Baltimore)*, vol. 45, no. 2, pp. 115–119, Feb. 2017, doi: 10.1016/j.mpmed.2016.12.001.

[14] L. Mohney and R. H. Lindberg, "Metabolic Encephalopathies | PM&R KnowledgeNow." Accessed: Nov. 28, 2025. [Online]. Available: https://now.aapmr.org/metabolic-encephalopathies/

[15] E. F. M. Wijdicks, "Identifying encephalopathies from acute metabolic derangements," ***J. Intern. Med.***, vol. 292, no. 6, pp. 846–857, 2022, doi: 10.1111/joim.13538.

[16] J. A. Frontera *et al.*, "Toxic Metabolic Encephalopathy in Hospitalized Patients with COVID-19," *Neurocrit. Care*, vol. 35, no. 3, pp. 693–706, 2021, doi: 10.1007/s12028-021-01220-5.

[17] L. Le Guennec, C. Marois, S. Demeret, E. F. M. Wijdicks, and N. Weiss, "Toxic-metabolic encephalopathy in adults: Critical discussion and pragmatical diagnostic approach," *Rev. Neurol. (Paris)*, vol. 178, no. 1–2, pp. 93–104, Jan. 2022, doi: 10.1016/j.neurol.2021.11.007.

[18] S. J. Jeon, S. S. Choi, H. Y. Kim, and I. K. Yu, "Acute Acquired Metabolic Encephalopathy Based on Diffusion MRI," ***Korean J. Radiol.***, vol. 22, no. 12, pp. 2034–2051, Dec. 2021, doi: 10.3348/kjr.2019.0303.

[19] R. Sonneville *et al.*, "The spectrum of sepsis-associated encephalopathy: a clinical perspective," *Crit. Care*, vol. 27, no. 1, p. 386, Oct. 2023, doi: 10.1186/s13054-023-04655-8.

[20] E. F. M. Wijdicks, "Hepatic Encephalopathy," ***N. Engl. J. Med.***, vol. 375, no. 17, pp. 1660–1670, Oct. 2016, doi: 10.1056/NEJMra1600561.

[21] T. h. Tranah, A. Paolino, and D. L. Shawcross, "Pathophysiological mechanisms of hepatic encephalopathy," *Clin. Liver Dis.*, vol. 5, no. 3, pp. 59–63, 2015, doi: 10.1002/cld.445.

[22] A. Jaffe, J. K. Lim, and S. S. Jakab, "Pathophysiology of Hepatic Encephalopathy," *Clin. Liver Dis.*, vol. 24, no. 2, pp. 175–188, May 2020, doi: 10.1016/j.cld.2020.01.002.

[23] J. A. González-Regueiro, M. F. H. la Tijera, R. Moreno-Alcántar, and A. Torre, "Pathophysiology of hepatic encephalopathy and future treatment options," *Rev. Gastroenterol. México*, vol. 84, no. 2, pp. 195–203, Apr. 2019, doi: 10.1016/j.rgmxen.2019.05.001.

[24] K. Lu, "Cellular Pathogenesis of Hepatic Encephalopathy: An Update," *Biomolecules*, vol. 13, no. 2, p. 396, Feb. 2023, doi: 10.3390/biom13020396.

[25] Y. Ntuli and D. L. Shawcross, "Infection, inflammation and hepatic encephalopathy from a clinical perspective," *Metab. Brain Dis.*, vol. 39, no. 8, pp. 1689–1703, Dec. 2024, doi: 10.1007/s11011-024-01402-y.

[26] R. P. C. Santos, E. C. D. B. Toscano, and M. A. Rachid, "Anti-inflammatory strategies for hepatic encephalopathy: preclinical studies," *Arq. Neuropsiquiatr.*, vol. 81, no. 07, pp. 656–669, Jul. 2023, doi: 10.1055/s-0043-1767819.

[27] D. R. Aldridge, E. J. Tranah, and D. L. Shawcross, "Pathogenesis of Hepatic Encephalopathy: Role of Ammonia and Systemic Inflammation," ***J. Clin. Exp. Hepatol.***, vol. 5, pp. S7–S20, Mar. 2015, doi: 10.1016/j.jceh.2014.06.004.

[28] A. Rocco, C. Sgamato, D. Compare, P. Coccoli, O. M. Nardone, and G. Nardone, "Gut Microbes and Hepatic Encephalopathy: From the Old Concepts to New Perspectives," *Front. Cell Dev. Biol.*, vol. 9, p. 748253, Nov. 2021, doi: 10.3389/fcell.2021.748253.

[29] A. K. Singal *et al.*, "ACG Clinical Guideline: Malnutrition and Nutritional Recommendations in Liver Disease," ***Off. J. Am. Coll. Gastroenterol***. *ACG*, vol. 120, no. 5, p. 950, May 2025, doi: 10.14309/ajg.0000000000003379.

[30] D. Bellafante, S. Gioia, J. Faccioli, O. Riggio, L. Ridola, and S. Nardelli, "Old and New Precipitants in Hepatic Encephalopathy: A New Look at a Field in Continuous Evolution," ***J. Clin. Med.***, vol. 12, no. 3, p. 1187, Feb. 2023, doi: 10.3390/jcm12031187.