

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

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Abstract.

Altered level of consciousness (ALOC) is a common clinical presentation in emergency and inpatient settings, with metabolic diseases representing as major etiologic causes. Among these, hepatic encephalopathy (HE) is one of the most frequent causes due to its high prevalence, morbidity, and mortality. HE has a complex pathophysiology mechanism involving neurotoxic substances such as ammonia. This narrative literature review discusses ALOC associated with metabolic disease, with emphasis on the underlying pathophysiological mechanisms of HE. Metabolic encephalopathy arises from systemic disturbances rather than primary structural brain injury and may progress to irreversible neuronal damage if untreated. HE develops in the context of acute liver failure, portosystemic shunting, or cirrhosis. Its pathogenesis reflects a multifactorial interaction involving hyperammonemia, systemic inflammation, gut microbiome dysbiosis, electrolyte disorders, malnutrition, sarcopenia, and manganese accumulation. Ammonia remains a central neurotoxin in HE, contributing to astrocytic swelling, glutamine accumulation, and cytotoxic edema. Inflammatory response further neuronal impairment through cytokine-mediated oxidative stress and blood-brain barrier disruption. Gut dysbiosis promotes bacterial translocation and endotoxemia, exacerbating systemic inflammation and worsening neurocognitive impairment. Given the broad differential diagnosis of ALOC, a structured clinical approach and early identification of metabolic causes especially HE is essential. Understanding the complex pathophysiological mechanism can provide optimized management and outcomes.

Keywords: *Altered level of consciousness, encephalopathy, metabolic disease and pathophysiology.*

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].

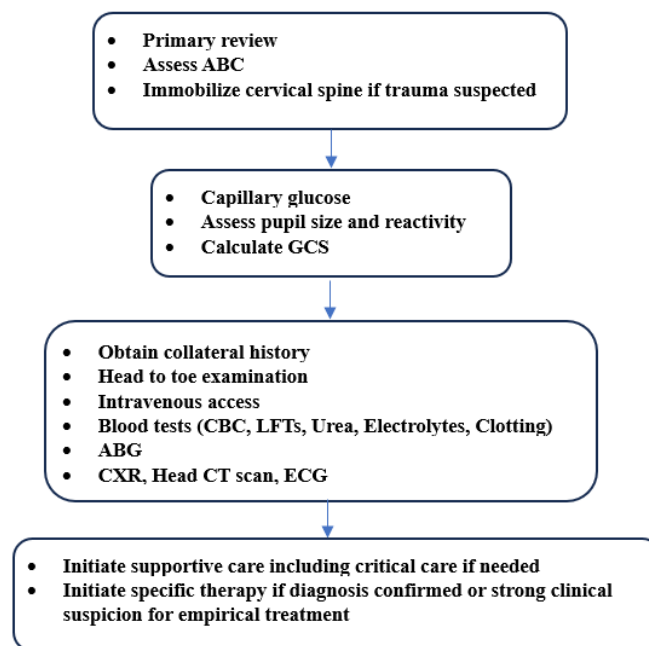


Fig. 1. Systematic Approaches to Altered Level of Consciousness Patient [4]

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-1 β 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 phylum *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 Enterobacteriaceae, while reducing commensal bacteria such as Lachnospiraceae [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].

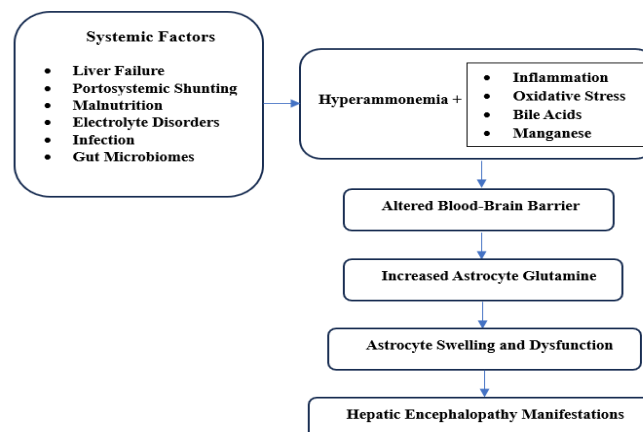


Fig. 2. Pathomechanism of Hepatic Encephalopathy.

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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