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Recent Perception About Hepatic Encephalopathy: A Review Article

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Graphic Abstract

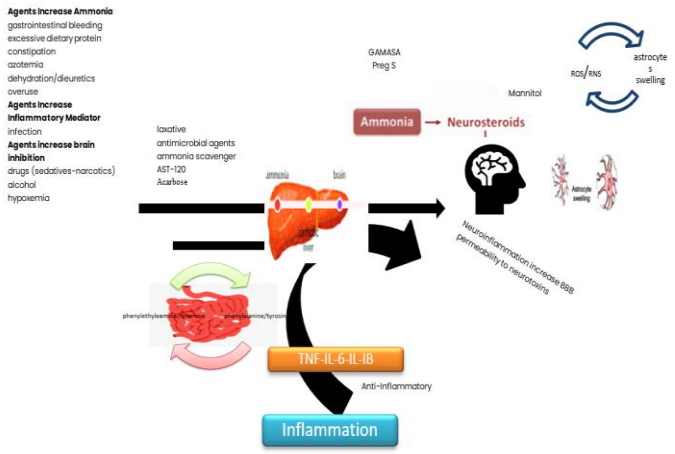

Fig -1: Different Strategies Could Contribute to Hepatic Encephalopathy

SUMMARY

Background

Hepatic encephalopathy (HE) has been defined as an adverse neurological consequence of hepatic decompensation. Hepatic encephalopathy can contribute to high fatality rate, and it has undesirable impact on different aspects of quality of life (QOL). Globally, HE has a high-ranking epidemiology. Therefore, it is a standpoint that requires extra research. the precise molecular mechanism of HE is still controversial. Hyperammonemia is regarded to be the most appropriate theory explaining the occurrence of HE until now is ammonia theory and this proposal reversed on the management approach and henceforth the outcomes.

Aim

This review aimed at giving a summary about HE with focusing on the new insight in HE pathophysiology and the pharmacological and non-pharmacological strategies.

Method

From December 2016 to March 2021, we conducted the study using various research engine such as Medline and PubMed. Different research terms as 'Hepatic encephalopathy, Ammonia, Inflammation' were used. All identified papers were full-text, and English-language papers. We also searched the reference lists of selected articles for additional related ones.

Results

The study revealed that there is an influential relationship between increasing ammonia level and existence of inflammation. Furthermore, the study convinced the synergism between hyperammonemia and inflammation in the pathogenesis of HE. Therefore, Agents with both ammonia decreasing effect and anti-inflammatory properties are superior to antibiotics in managing of HE.

Conclusion

Reversing inflammation is beneficial to maintain the blood brain barrier integrity and prevent the entry of toxic mediators into the brain. New targets should be established, and a combination of anti-

inflammatory agent and ammonia-lowering agent should be used as first line therapy in the management of HE.

***Keywords*:** Hepatic Encephalopathy – decompensation - inflammation-liver.

1. INTRODUCTION

Hepatic encephalopathy is the furthermost prevalent neurological complication of liver insufficiency (1). Patients having hepatic encephalopathy suffers from mental changes and motor disorders (2). The range of neuropsychiatric defects such as incomprehension, confusion, personality changes, and loss of consciousness can vary according to severity, acuity, and time course (3,4). Corresponding the etiology, HE can be classified into three types; Type A which is associated with acute liver failure (ALF) and may be a result of paracetamol toxicity (the common cause of ALF in USA), viral hepatitis (the common cause in developing countries) or unknown cause. type A HE is characterized by a rapid onset approximately two months or less and is characterized by a high-grade edema that necessitate liver transplantation to offset the liver failure and maintain the survival. Type B HE which caused by portosystemic shunts without intrinsic liver disease, and type C HE that linked to liver cirrhosis and characterized by delayed onset usually more than 6 months and persistent neuropsychiatric sequalae. Based on clinical symptoms, HE can be divided into two large categories; covert HE in which patients presented with unnoticeable mental changes but has cognitive deficit in specific neuro-psychometric test and overt HE which is the apparent form of HE and in which patients suffer from decline in the mental and motor function. Rendering the severity and based on patients' behavioral symptoms and clinical signs of mental obtundation, HE can be further divided into five grades according to west heaven criteria from grade 0 in which patient is normal upon clinical examination but appear abnormal upon psychometric test performing to grade IV in which patient is comatosed (5,6).

Epidemiology

Approximately 60% of cirrhotic patients develop some degree of HE and its occurrence represents poor prognostic indicator(7). HE is accounting for more than one hundred thousand yearly hospital admission with total costs of around seven billion dollars and a massive family burden (8). HE is more common in elderly and has the maximum occurrence in the united states (9) .

Precipitating agents

Many triggering mediators may contribute to the occurrence of HE particularly those which increase ammonia and inflammation. The more the co-existing risk factors, the higher the grade of hepatic encephalopathy (10).

2. RECENT ADVANCES IN HE PATHOGENESIS

Pathophysiology of HE is sophisticated, and the most established principle is hyperammonemia despite its drawbacks. However, a wide range of theories had been discussed such as manganese deposition, systemic inflammation, and false neurotransmitters theories. Moreover, genetic mutation and coroid plexus function alteration are new acceptable theories for explanation of HE pathogenesis and should be given more attention in respect to term of treatment (11).

Ammonia: Colonic microbes and mucosal enzymes destroys dietary proteins into ammonia. Ammonia bypasses the cirrhotic liver to the brain and converted into glutamine in astrocytes causing many physiological trouble and astrocyte swelling. Astrocyte swelling activates reactive nitrogen/oxygen species (RNOS) synthesis which in turn encourage astrocyte swelling in a rancorous cycle and induce HE. Sustained exposure to ammonia triggers taurine and myoinositol release, disables glutamine transponder and downregulate glutamine receptors as a compensatory

mechanism to counter glutamine effect. Unfortunately, these changes over times modify the brain shape and form and at last lead to Alzheimer type II. In addition, ammonia hasten the astrocyte Senescence and senescence gene stimulation inhibition of astrocytes proliferation leading to inhibition of the brain function. Interestingly, chronic hyperammonemia boosts serotonin turnover and causes altered sleep pattern. Likewise, ammonia worsen brain energy metabolism and blood flow (12,13). On the other hand, Ammonia theory has some significant limitations such as about 10% of patients with HE has normal serum ammonia, the ammonia level is not relational to the grade of HE and not associated with HE prognosis, many cirrhotic patients have high ammonia level without sign for HE and ammonia metabolism is significantly influenced by other organs, such as the kidneys, muscles, brain, and bowel(14). More remarkably, management of HE with lactulose was not affected by the existence of ammonia or its level, demonstrating that ammonia level does not guide therapy in clinical practice (15). for the previous reason, the ideal treatment strategy should not focus only on reducing ammonia level and further targets for HE treats must be discussed.

Inflammation and blood brain barrier permeability:

Cirrhotic patients generally suffer from impaired host defense mechanisms and more vulnerable to catch infection. The peripheral immune system and the brain cooperate in response to infection and inflammation. While astrocytes and microglial cells release cytokines to fight injury or inflammation, the high level of TNF-α stimulates glial cells to secrete the cytokines Il-1 and Il-6, TNF-α, and Il-1β. Inflammatory mediators affect the integrity of the BBB, enhance fluid phase permeability of the brain, and facilitate the diffusion of ammonia and other neurotoxin into astrocytes. Exaggerated systemic inflammatory response syndrome (SIRS) overcome the innate compensatory 'anti-inflammatory responses' (CARS) leading to cerebral damage and neural dysfunction. Systemic inflammation drives a broad range of behavioral alterations ranging from mild changes to complete coma (16,17). Neurological Disorders of HE is primarily astroglial however neuron focal loss may also occur in the basal ganglia, thalamus, and cerebellum. Inflammation theory has many strength points since the circulating levels of TNF-α are always increased in cirrhotic patients and the increase predicts the HE occurrence, determines the severity of episodes, and strongly correlates with HE grades. in addition, cells exposed to TNF-α show obvious increasing in ammonia transporting and modulate the effect of ammonia on the brain. Additionally, high level of ammonia generated substantial a remarkable decline in neuropsychological test scores when evidence existed for inflammatory state. Moreover, the grade III and grade IV encephalopathy is highly evidenced in the presence of SIRS and not with ammonia (18). Based on the above-mentioned evidence of the important role of inflammation in HE pathogenesis, reversing inflammation appear to be essential targets in the management of HE.

False neurotransmitters: There is a balanced ratio between branched chain amino acids (BCAA) and aromatic amino acids (AAA) known as Fischer ratio which is maintained by normal hepatic metabolism of amino acids. In case of liver cirrhosis the metabolism of BCAA such as isoleucine, leucine, and valine takes place in muscle where it can countersign ammonia clearance by stimulating protein synthesis (19). In contrast, AAA cannot be metabolized in muscle and consequently it passes into the brain and act as precursor to false neurotransmitter synthesis. False neurotransmitters share structural resemblance with normal neurotransmitters but lacks pharmacological action thus they can block normal catecholamine activation producing brain depression and HE. False neurotransmitters might also be formed in GIT by the action of bacteria on proteins and enter the

systemic circulation through portal-systemic shunts and make their way to the brain (20).

Manganese and Neurosteroids: Elevated level of manganese is common in chronic liver diseases and the deposition of manganese in the basal ganglia in cirrhotic patients simply detected as pallidal MRI signal hyperintensity is responsible for the parkinsonian signs of HE such as tremor. Manganese as neurotoxin can induce changes in astrocytes of the basal ganglia that promote the formation of alzheimer type II. Besides, manganese deposition predisposes GABAenergic tone boost that could be a result of increasing ammonia level and neurosteroid synthesis (21,22). Manganese increases the expression of the translocator protein called peripheral type benzodiazepine receptor 18kDa that located on the mitochondrial membrane of microglial cells and governs the neurosteroid synthesis in the endoplasmic reticulum from cholesterol precursor. Neurosteroids as allopregnanolone and tetra hydroxy progesterone increase the chloride ions influx and act as positive allosteric modulators of the membrane receptors (GABA-A receptors and 5-HT_3 receptors) and nuclear receptors (progesterone receptors and glucocorticoid receptors) along with serotonin receptors modulation and thus alter the neurotransmission with subsequent precipitation of HE(23,24).

Brain energy metabolism and Bile acid level: Impairment in cerebral energy metabolism including alterations in glucose consumption, and glycolysis together with mitochondrial dysfunction is responsible for the neurological alterations in HE. Increased brain lactates due to either an increase in astrocyte production or a decrease in neuronal uptake is a primary player in the pathogenesis of brain edema and neural cell death in many neurodegenerative diseases such as HE(25). expanded blood-brain barrier permeability and changes in ASBT; apical sodium-dependent bile acid transporter in the choroid plexus enables the access of bile acids to the brain(26). Bile acids cause cognitive deficit by activation of Farnesoid X receptor (FXR): a nuclear bile acid receptor-mediated signaling in the frontal cortex and increases the pro-inflammatory CCL2 expression by activation of sphingosine-1-phosphate receptor 2 (S1P2R) in neurons. TGR5 represents another receptor target for bile acid(27-28).

3.LATEST ADVANCES IN HEPATIC ENCEPHALOPATHY DIAGNOSIS

The main approach to HE diagnosis is excluding other possible causes of encephalopathy in combination with recognizing the precipitating factors and confirming the diagnosis by clinical picture, a positive response to empiric treatment and using neuro-psychometric tests.

Psychometric test

The PHES-psychometric hepatic encephalopathy score-is the gold standard for minimal HE diagnosis and acts as a useful prognostic tool for forecasting the converting to OHE and predicting the survival. The PHES test is used globally as it can evaluate motor speed, visual perception, attention, and memory. Abnormality of more than two standard deviations from the mean in two or more tests is diagnostic for MHE (29). Repeatable Battery for the estimation of Neuropsychological Status (RBANS) is the alternative test to PHES test and it is useful in the determination of working memory, intellectual processing speed, language, and visual function. Inappropriately, paper and pencil tests (PHES and BRANS) are time consuming and difficult to be interpreted therefore, the computer-aided psychometric tests, like the scan test, Cognitive Drug Research assessment test (CDR), inhibitory control test (ICT), EncephalApp Stroop have been used as a replacement for(30). Apart from these above-mentioned tests, The EncephalApp Stroop is a valid

and rapid test consume 5 minutes on any Apple or Android device and is free to download for HE diagnosis but lack discrimination between grade I & grade II HE. the Critical Flicker Frequency (CFF) is a neurophysiological test used in HE diagnosis with high specificity (55%) and sensitivity (99%). CFF is a convenient test widely used in clinical trials as it is not influenced neither by age nor educational status and is based only on the ability of a human brain to distinguish flickering light as discrete light pulsations. Moreover, it needs binocular vision and is expensive. Electroencephalography (EEG) is another neurophysiological test complementary to neuroimaging used in the assessment of MHE and is more objective than psychometric tests, EEG is used to detect changes in cortical cerebral activity across the wide spectrum of HE. However, it is nonspecific and may be influenced by associated metabolic disturbances. EEG requires an institutional setup and neurological expertise in evaluation besides the high cost(31). According to the current guidelines, using a combination of tests is preferred to ensure impairment and establish HE diagnosis (29).

4.NEUROIMAGING TECHNIQUE IN HEPATIC ENCEPHALOPATHY

Although neuropsychiatric and neurophysiologic tests are critical in, HE diagnosis, the imaging techniques are very important in simplifying the pathophysiology of HE.

Magnetic resonance image (MRI) can exclude another encephalopathy such a Wernicke's encephalopathy, viral encephalitis, and stroke and can detect brain abnormalities present in HE such as brain edema, brain atrophy induced by ammonia. Consequently, it is expected that MR imaging will be progressively used to assess the mechanisms complicated in the pathogenesis of HE and to appraise the consequences of therapeutic approaches focused on adjusting brain edema in these patients (32).

Computed tomography (CT) can exclude other reasons for brain dysfunction including intracranial hemorrhage, infarction, infection, or tumor and its indication for cirrhotic patients is only useful for those have neurological focus (33). Positron emitting technique (PET) provides information about anatomy and function of the brain and can detect the potential pathophysiology of HE. PET assesses the glucose and ammonia metabolism, cerebral blood flow, neuroinflammation, BBB permeability, peripheral benzodiazepine receptors (PTBR), and changes in different neurotransmission system in patients with differing degrees of HE, patients with MHE or type C HE (34). Lumbar puncture analysis of CSF is often used to exclude other comorbidities in patients with HE as meningitis, encephalitis, and subarachnoid hemorrhage but not to confirm a diagnosis and it is contraindicated in patients with severe coagulopathy due to risk of bleeding and also is prohibited in patients with acute liver failure because of the risk of cerebral edema, increased intracranial pressure and brainstem herniation owing to the procedure (35).

Management of HE

Avoiding risk factors is the primary prophylaxis to prevent OHE recurrence and Secondary prophylaxis should be initiated after an episode of OHE. However, patients who have liver failure and intractable overt HE should be referred for liver transplantation (36).

5. NONPHARMACOLOGICAL TREATMENT

No less than 80% of patients with OHE improve after correction of the precipitating factors. Correction of infection by IV antibiotics especially third generation cephalosporins besides prevention of constipation, electrolyte imbalance, and upper GIT bleeding is important for prophylaxis of HE. Cirrhosis screening, hepatitis B vaccination, and treatment of hepatitis C will diminish cirrhosis and hence prevent HE. Around 70% of patients with HE has moderate to severe

protein-calorie malnutrition. Patients with OHE should have approximately 40 kcal/kg from dairy protein with increased intake of vegetable fiber to encourage ammonia clearance via defecation. Dietary protein limitation is not counselled since the loss of lean mass produces ammonia and exacerbates HE Hence, patients with HE are recommended to eat small meals consistently delivered during the day including a late-night super and avoid deprivation for longer than 3–6 h during daytime to create positive nitrogen balance that promotes hepatic regeneration and increases ammonia detoxification capacity (37). cirrhotic patients with sustained malnutrition and sarcopenia show an elevation in the resting metabolic rate/lean body mass and reduction in hepatic glycogen storage so the body switches to gluconeogenesis from amino acids and lipolysis and this consumption of blood amino acids promotes proteolysis, skeletal muscle wasting and increased ammonia production. Therefore, parenteral nutrition in patients with a fault of swallowing and cough reflexes, and the unprotected airway are compulsory. Zinc is an essesntial cofactor for urea cycle enzymes and administration of zinc sulfate at 220 mg twice daily may also improve dysgeusia and muscle cramping so used as a complementary treatment in hepatic encephalopathy(38). Fecal microbiota transplantation (FMT) and prebiotics modify the gut microbiome and deemed as safe and efficacious in preventing gut dysbiosis and bacterial translocation hence it protects from endotoxemia and systemic inflammation (35). Prebiotics as Lactobacillus SF68 contains live microorganisms with probable beneficial effects on gut dysbiosis so it can lower the level of ammonia, improve HE recovery, and better the quality of life. Molecular adsorbent recirculating system (MARS) is an extracorporeal liver support technique that uses hemodialysis in combination with adsorbent such as charcoal or albumin and used to enable the dialysis of albumin-bound toxin (bilirubin-bile acids-tryptophan-fatty acids-TNF-copper-benzodiazepine) and water-soluble toxins as(ammonia-urea-creatinine) and can reduce inflammatory mediators such as interleukin (IL)- 8 and IL-6 with subsequent reverse the massive inflammatory process and improve symptoms and clinical features in patients with severe encephalopathy as well as act as a bridge while waiting for transplantation (39). Starting of peritoneal dialysis is useful in patients with HE with or without end stage liver disease (ESRD) by lowering blood ammonia levels, preventing recurrence of encephalopathy episodes, and rebuilding the patient's functional status and quality of life (40). Plasmapheresis appears to improve the stage of HE in particular refractory hepatic encephalopathy by minimizing innate immune activation and alleviation of multiorgan dysfunction(41). Delivering glutamine synthetase GS gene is a hopeful alternative treatment of hyperammonemia in HE that lacks the need for clinical interventions with potential secondary effects and relapses common with traditional therapies (42). The definitive solution for recurrent and intractable HE is liver transplantation and the cognitive disturbance associated with HE reversed 5 years after transplantation.

6. PHARMACOLOGICAL TREATMENT

Ammonia-Lowering Agents

Non-absorbable disaccharides as lactulose are the primary treatment for OHE. Lactulose may be continued for lifetime in patients with recurrent episodes since it displays wide safety and tolerability with minor side effects as abdominal cramping and diarrhea. Lactulose is broken down by bacteria in the colon to two components lactic acid and acetic acid which reduces colonic pH, decreases urease liberating bacteria in the gut and facilitates the conversion of ammonia (NH_3) to ammonium (NH_4^+) which is less readily absorbed by the gut. Also, its cathartic effect increases fecal nitrogen waste. Administration of 25 mL lactulose orally every two or three hours as starting dose helps to achieve two or more soft stool. For

comatosed patients, nasogastric or rectal lactulose administration is more convenient option and once the patient is awake oral lactulose therapy is started(43). Polyethylene glycol is a purgative laxative agent which is superior to lactulose in improving HE with a quicker time for resolution(44).

The second line therapy is antimicrobial agent which reduces the bacterial production of ammonia via turning the harmful gut microbiota to a more beneficial one. Rifaximin is slightly absorbed and possesses a wide activity against both gram-positive, gram-negative aerobic as well as anaerobic bacteria. RFX is used for treating HE in combination with lactulose to attain better remission and decrease the frequency of re-admission. Neomycin blocks ammonia genesis of bacteria by obstructing the glutaminase enzyme which is responsible for converting glutamine to ammonia, and it is effective in HE treatment, but it has major potential adverse effects including ototoxicity as well as nephrotoxicity limit its clinical use. Metronidazole targets the treatment of gram-negative anaerobic gut bacteria that produces urease. Therefore, it decreases ammonia production. However, long-term use of metronidazole is associated with possible neurotoxicity that limits its routine use(45). Recently nitazoxanide seems to be suitable alternative to rifaximin in preventing HE recurrence depending on its ammonia-lowering action and its anti-inflammatory properties(46). Decreased Fischer ratio in cirrhotic patient predisposes hepatic encephalopathy and the oral BCAAs administration may be used as monotherapy or add-on agent in the treatment of patients with HE especially in people with poor response to lactulose and rifaximin combination therapy(47). L-Ornithine L-Aspartate (LOLA) transfers ammonia into urea and/or glutamine, decreases the extent of blood ammonia, improves the mental state, PHES and HRQOL (48). The therapy has bit side effects like vomiting, cough, and diarrhea and these side effects increased with IV administration(49). Ornithine/ phenylacetate (PAA) crystalline combination decreases plasma NH3, stimulates the removal of ammonia in the form of urinary poly acetate glutamine PAGN by normalizing glutamine synthetase, and reduce brain edema and intracranial hypertension. It is safe and tolerable with no severe adverse evenents(50). Sodium benzoate, sodium phenylbutyrate, and sodium phenylacetate convert ammonia into hippuric acid which is readily excreted in the urine hence, these drugs are recommended for patients with urea cycle enzyme defects and HE but pay attention to Sodium as it results in a high sodium load(51). Acarbose is an intestinal α-glucosidase inhibitor used to treat type 2 diabetes mellitus, acarbose inhibits intestinal glucose absorption and results in their enhanced delivery to the colon so the ratio of intestinal saccharolytic to proteolytic bacterial flora is increased thereby stimulates gut motility and reduces ammonia production and improves mild hepatic encephalopathy in cirrhotic diabetic patients(52) Zinc is a cofactor for urea cycle enzymes by increasing the activity of ornithine transcarbamylase, and this is important in ammonia detoxification, Treatment with zinc sulfate at 220 mg twice daily may also improve dysgeusia and muscle cramping so used as a complementary treatment in hepatic encephalopathy (53). Acetyl-L-carnitine stimulates urea synthesis causing a decreased level of ammonia in both the blood and the brain and improves neuropsychological activities (visual scanning, psychomotor speed, mental flexibility, language short-term memory, and computing ability), reduces the severity of mental and physical exhaustion beside its good impact on health-related quality of life(54).

7. ANTI – INFLAMMATORY AGENTS

Systemic inflammation and ammonia are synergistic in the pathogenesis of HE so anti-inflammatory therapy will reduce systemic and brain inflammation (55), ibuprofen (IBU) and minocycline (MINO) improve the BBB integrity, reduce the hippocampal apoptosis, recover memory loss and reverse the long term potentiation

(LTP) impairment in the hepatic encephalopathy. Patients with advanced liver disease are prone to infection as they have an impairment of host defense mechanisms. The administration of ibuprofen stabilizes cyclooxygenase along with inducible NO synthase activities and reverse the learning difficulties and cognitive impairment in HE patients. Toll-like receptor (TLR) is one of the pathogen recognition receptors (PRRs) family and it is a part of the immune system which can identify pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) relevant to foreign invading particles, host cells activation of this receptor initiate the expression of various target genes including inflammatory cytokines, chemokines, and interferons-1 (IFNs)(55). The discharge of DAMPs and PAMPs from injured hepatocytes and bacterial translocation due to cirrhosis stimulates inflammatory processes through a TLR4-NFκB mechanism on Kupffer cell and TLRs antagonist will block this inflammatory process and improve HE(56).

8.OTHER TREATMENT

GABAA Receptor Modulating Steroid Antagonists (GAMSAs) decrease the neurosteroids effects, increases alertness and cognition in patients with HE, improve the learning function and restore motor coordination and memory(57). Pregnenolone Sulfate (PregS) improves cognitive and motor coordination alterations in patients with MHE and improves the QOL by modifying both GABAergic tone and NMDA receptor, liposomes or nanoconjugates systems should be used to introduce PregS into the brain(58). spherical Carbon (AST-120): is an orally administered engineered carbon microsphere with a huge surface area to adsorb ammonia and other neurotoxic and hepatotoxic agents from GIT. Additionally, Spherical carbon is used to decrease uremia by decreasing intestinal indole absorption and consequently indoxyl sulfate production, decreases oxidative stress, and resolves brain edema in HE patients(59). Cholestyramine attenuates the activation of microglia by bile acid sequestrating effect and used in pruritis treatment(60). Human albumin solution (HAS) has antioxidant and inflammatory properties as it binds endogenous and exogenous toxins and has been used as a volume expander in cirrhosis, HAS also show activity in preventing HE(61). BBD is a special Chinese formula that prevents and cures hepatic encephalopathy (HE) by reducing hyperammonemia and systemic and neurological inflammation. Inflammation is probabl e an important target of BBD by regulation of the TLR4/MyD88/NF-κ B pathways(62). presence of ammonia in astrocytes induces intracellular calcium elevation which in turn activates free radicals formation, BAPTA-AM is a Ca2+ chelator used to lessen this increase in calcium within the brain(63). glutamine synthetase inhibitor, cNOS inhibitor (7-nitroindazole), and NOX inhibitor (apocyanin) significantly block ammonia-induced free radical production and inhibit astrocyte senescence (64).

9. CONCLUSION

Inflammation can affect the brain directly by releasing of pro-inflammatory or indirectly by increasing blood brain barrier permeability and allowing the diffusion of ammonia and other neurotoxin into the brain so anti-inflammatory agent should be used as an adjuvant therapy to antimicrobial agents as first line therapy of HE.

AUTHORSHIP

Author contributions: All authors contributed towards study design, research/literature collation, writing of the manuscript, formulating, and critical revision.

DECLARATION OF PERSONAL INTERESTS

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