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OVERVIEW OF HEPATIC ENCEPHALOPATHY

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Abstract:

Introduction: *Chronic liver disease and cirrhosis affect millions of patients all over the world. The vast majority of patients develop various complication related to portal hypertension. About 30-45% of patients with cirrhosis are known to suffer from hepatic encephalopathy. Hepatic encephalopathy (HE) is one recurrent complication, a reversible syndrome of impaired brain function, causes by a neurotoxin, impaired neurotransmission due to metabolic changed in liver failure, systemic inflammatory response, changed in brain energy metabolism and alteration in the blood-brain barrier. The manifests in a wide variety of neurological and psychiatric problems including personality changed, progressive disorientation in time and space, alterations in consciousness, stupor, and coma in the final stage. Treatment may include palliative therapies, correcting precipitating factors, lactulose or rifaximin.*

The aim of Work: *The study aims to give an overview of hepatic encephalopathy including the pathophysiology, etiological factors, diagnosis and treatment modalities.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Chronic liver disease, hepatic encephalopathy, pathophysiology, management strategy*

Conclusion: *Cirrhosis and its complication remain as one of the major problems in the healthcare system all over the world. With the rapid spread of metabolic syndrome and non-alcoholic steatohepatitis induced cirrhosis, management of complications of cirrhosis has become more economically burdensome. Despite clinical trials and research, the pathogenesis of HE remains to be clarified more for more effective treatment options.*

Keywords: *Chronic liver disease, hepatic encephalopathy, pathophysiology, management strategy.*

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INTRODUCTION:

Chronic liver disease and cirrhosis affect millions of patients all over the world. The vast majority of patients develop various complication related to portal hypertension. About 30-45% of patients with cirrhosis are known to suffer from hepatic encephalopathy. Hepatic encephalopathy (HE) is one recurrent complication, a reversible syndrome of impaired brain function, causes by a neurotoxin, impaired neurotransmission due to metabolic changed in liver failure, systemic inflammatory response, changed in brain energy metabolism and alteration in the blood-brain barrier. The manifests in a wide variety of neurological and psychiatric problems including personality changed, progressive disorientation in time and space, alterations in consciousness, stupor, and coma in the final stage. Treatment may include palliative therapies, correcting precipitating factors, lactulose or rifaximin.

Hepatic encephalopathy is on the adverse complication of cirrhosis which severely affects the lives of many patients and includes various neuropsychiatric abnormalities, liver dysfunction, and portosystemic shunting. [1]

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Chronic liver disease, hepatic encephalopathy, pathophysiology, management strategy

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Pathophysiology

Pathophysiology of HE is multifactorial ranging from neurotoxins to systemic infection and inflammation. There are various agents known to involve in pathogenesis are ammonia (NH_3), inflammatory cytokines, manganese deposition in basal ganglia and benzodiazepine-like compounds such as gamma-aminobutyric acid (GABA), certain microbiota and aromatic acids are also contributing a role in pathogenesis. Though there are multiple factors, include, ammonia remains the primary pathophysiological factor of HE. [1,2]

Neurotoxin

NH_3 is a nitrogenous gut-derived product such as enterocytes from glutamine, produced by bacterial metabolism of urea from proteins consumed in the diet and is best-characterized neurotoxin linked to HE. [3] NH3 is metabolized by the liver and cleared by kidneys and to some extent by muscles. Cirrhotic patients have impaired hepatic metabolism of NH_3 due to liver dysfunction, results in shunting of NH_3 – rich portal blood to systemic circulation without detoxification. When NH_3 crossed the blood-brain barrier, it is metabolized in astrocytes by glutamine synthetase, which converts NH_3 and glutamate to glutamine. An osmotic gradient is formed as a result of the accumulation of glutamine in astrocytes resulting in its swelling which leads to the generation of reactive oxygen resulting in cerebral dysfunction. Thus, swelling of astrocytes as a consequence of hyperammonemia is a key event in the development of HE. [1,2,4]

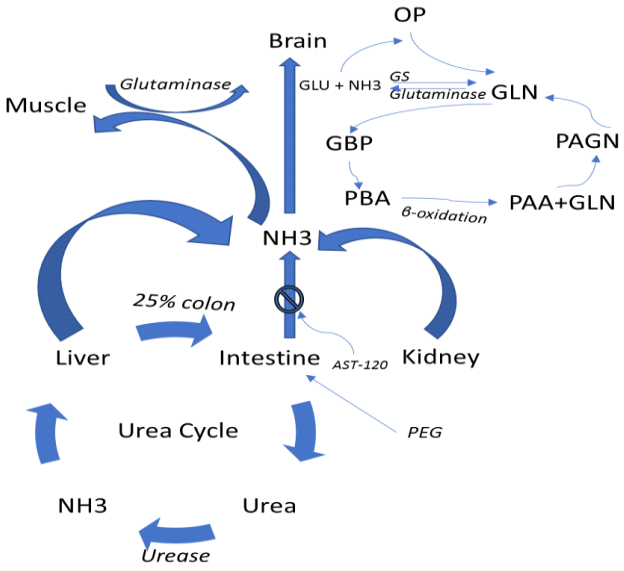

Fig 1: Urea Pathway

Systemic Infection and Neuroinflammation

Another causative factor of brain dysfunction is an alteration in cerebral blood flow and release of inflammatory mediators which in turn is occurring due to direct infection of brain tissue.[5] The systemic inflammatory response syndrome is the result of release and circulation of pro-inflammatory cytokines and mediators. These cytokines include tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), IL-6 and IL-18. These mediators also potentiate the effect of ammonia on CNS, decrease the brain myoinositol and increase in brain water.[6,7]Sepsis due to encephalopathy is characterized by a change in mental status and motor activity from delirium to coma.[8]

Impairment in Neurotransmission

Various experimental models have been studies in acute liver failure with the investigation of neurochemical, neurobehavioral and electrophysiological methods. Most studies showed change*d* in GABA-benzodiazepine-ergic, dopaminergic, serotoninergic and glutamate-ergic neurotransmitter system.[9,10] The most potent positive allosteric modulator of the GABAA receptor complex are neurosteroids(Allopregnanolone and pregnenolone)with its significantly increased concentration in the brain with hepatic coma, patients. Activation of astrocytic 18-kDa translocator protein contributes to the pathogenesis of CNS symptoms of HE.[11,12]

Classification

HE can be classified by a various factor such as [13]

According to underlying Disease	According to Severity of Manifestation	According to Time of Course	According to Precipitating Factors
• **Type A**- due to acute liver failure • **Type B**-due to portosystemic bypass or shunting • **Type C**-due to cirrhosis	**West-Haven criteria (WHC)** • Grade 0 • Grade I • Grade II Over • Grade III • Grade IV	• **Episodic** • **Recurrent** – occurring in a time interval of less than or equal to six months. • **Persistent** – a pattern of behavioral alteration is always present with relapse.	• **Non-precipitated** • **Precipitated-** Precipitating factors are listed below.

Table 1: classification of hepatic encephalopathy

Clinical Manifestation

In advanced liver dysfunction, various systems and their functions are affected and impaired including CNS which manifests in HE. The impairment remains subclinical for a prolonged time in early stages. The precipitating factors which disrupt liver function are as follow: [14]

- Increased nitrogen load: Gastrointestinal bleeding, constipation, Renal failure, Blood transfusion
- Metabolic: Hypovolemia, Hypokalemia, Metabolic alkalosis, Hyponatremia, Hypoxia, Hypoglycemia, Anemia,
- Increased systemic stress: Infection and surgery
- Vascular: Portosystemic shunts (surgical or TIPS), Vascular occlusion (hepatic vein or portal vein thrombosis)
- Medication: sedatives, tranquilizers, narcotics, hepatotoxic agents.

Patients with subclinical or minimal HE has disturbances detected only on neuropsychiatric and psychomotor testing while overt HE may present with coma. The most common early manifestation is a disturbance in diurnal sleep pattern related to melatonin secretion. Advanced neurological features are bradykinesia, asterixis, hyperreflexia, and transient decerebrate posturing. Rarely HE may present with hemiplegia. [14]

The clinical feature of HE by severity is presented as different grades by West Haven Classification as follows: [15]

- **Grade 0** – Minimal hepatic encephalopathy, minimal changes in memory, concentration, intellectual function, and coordination. Asterixis is absent
- **Grade I** –Mild lack of awareness, mild confusion, shortened attention span, ability to perform mental tasks, hypersomnia, insomnia, inversion of sleep pattern. Asterixis can be detected
- **Grade II** –Lethargy or apathy, disorientation, inappropriate behavior, slurred speed, drowsiness, lethargy, deficit ability to perform mental tasks, obvious personality changes. Frank asterixis
- **Grade III** – somnolence, inability to perform mental tasks, disorientation to time and place, marked confusion. Frank asterixis
- **Grade IV** –Coma with or without response to painful stimuli. Absent asterixis.

Diagnosis and treatment

The primary diagnosis can be made exclusion criteria. Based on the presence of neuropsychiatric abnormalities with liver dysfunction after exclusion of unrelated neurologic and metabolic causes of encephalopathy. The possible differential diagnosis are as follows:[14]

- Metabolic encephalopathy: Hypoglycemia, Hyponatremia, Hypoxia, Uremia, Ketoacidosis
- Intoxication: Alcohol, sedatives, narcotics, hypnotics, anti-depressant, neuroleptics
- Alcohol withdrawal
- Wernicke encephalopathy
- Hyperammonemia due to Renal failure, urinary tract infection, severe muscle exertion, gastrointestinal bleeding
- Organic CNS diseases: subdural hematoma, intracranial bleeding, stroke, abscess, tumor, meningitis, encephalitis, organic brain syndrome

The imaging modalities include computed tomography (CT), Magnetic resonance imaging(MRI), electroencephalography(EEG). Laboratory abnormalities can indicate liver diseases such as elevated bilirubin, alanine, aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate, the international normalized ratio (INR), decrease serum albumin level, electrolyte disturbance associated with portal hypertension or the use of diuretics. Elevated serum and arterial ammonia levels. [16] There are different psychometric and neuropsychiatric tests present to detect the minor deficits in mental function however these tests are not specific to HE and other forms of encephalopathy. The various other tests are number connection test (NCT), Inhibitory control test (ICT), the Stroop test, critical flicker frequency test. [17,18]

General principles in treatment include controlling of precipitating factors, 90% of patients can be treated with the management of precipitating factors itself. Specific drug treatment is a part of management. Non-absorbable disaccharides (Lactulose) is used in the initial treatment of HE [19], dosing should be initiated with 25 milliliters every 1-2 hours until two soft or loose bowel movement produced per day. Various antibiotics have been used for HE therapy such as Rifaximin (can be used for a long-term therapy), Neomycin (glutaminase inhibitor), Metronidazole (for short term therapy) Many other drugs have been used for treatment such as Probiotics ,laxatives BCAA (branched chained amino-acid) improve the manifestation of episodic HE 93. Metabolic ammonia scavengers are used for the treatment of inborn errors such as urea cycle, most commonly used Ornithine phenylacetate and Glyceryl phenylbutyrate can be used for episodic HE for over 6 months. Flumazenil is not a frequently used drug but improves mental status in overt HE.[20]

Approach for addressing a patient with HE:

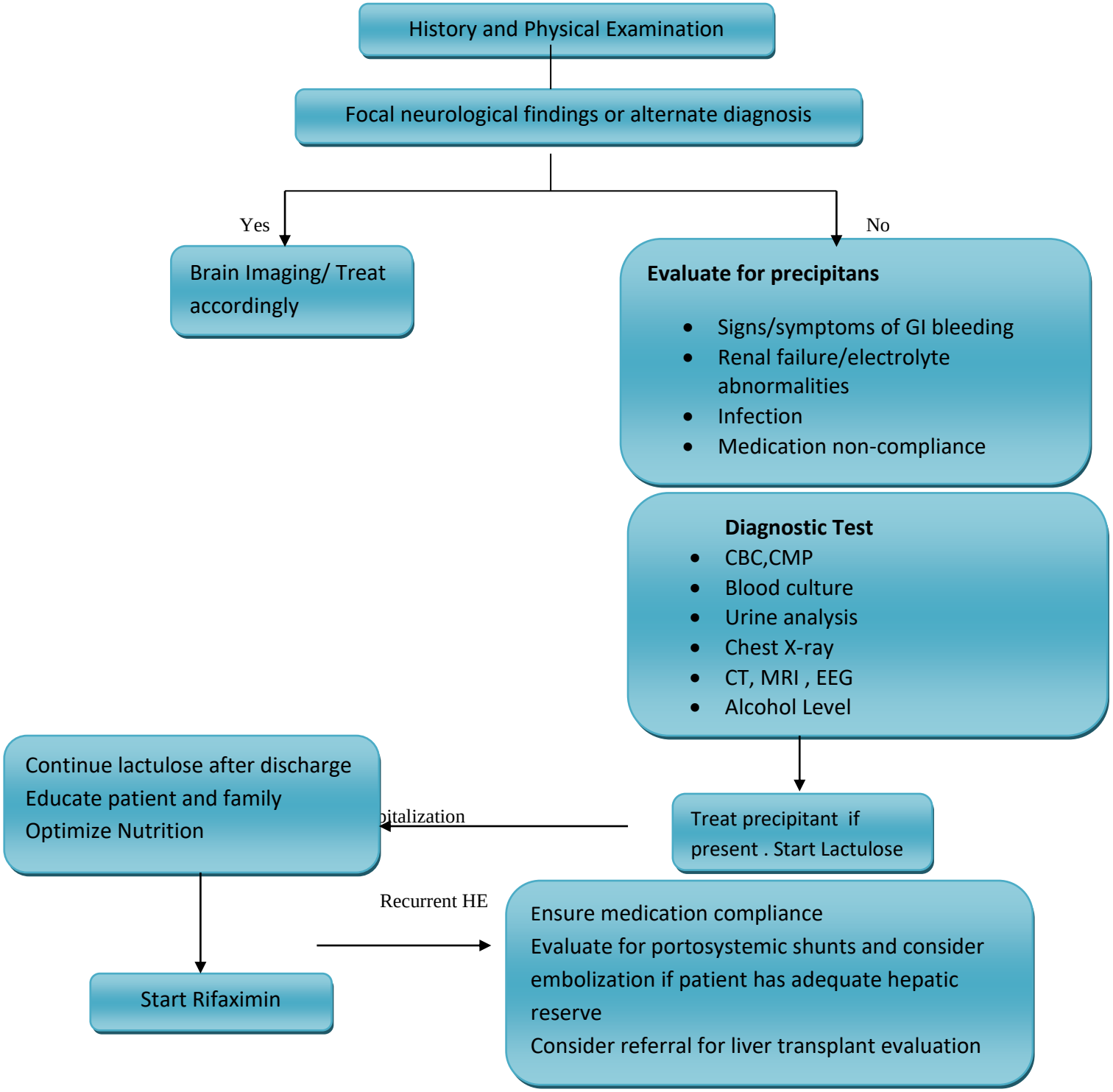

Fig 2: Approach for addressing a patient with hepatic encephalopathy [21]

CONCLUSION:

Hepatic encephalopathy is a common but reversible neuropsychiatric problem in patients with cirrhosis and portosystemic shunting. HE has significant morbidity and mortality as well as health care costs. Thus, the correct approach to diagnosis and treatment plan is essential by ruling out and correcting or limiting underlying precipitating factors, treating with non-absorbable disaccharides, antibiotics, probiotics, BCAAs and also educating the family members on how to respond to initial measures.

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