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Diagnosis and Management of Encephalopathy in Emergency Department

[1]Fatimah abdullah alyousif, [2]Hawra Hassan Alkhatem, [3]Safa A. Alabdaljabbar

Abstract: **This article aims to help with recognition and management of HE in the emergency department (ED) by reviewing its pathogenesis, classification, diagnosis, grading, and treatment. A comprehensive search was conducted through major databases; Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, through November, 2017. The search strategy used Mesh terms; encephalopathy, emergency department, management. HE is a typical and significant complication of chronic or acute liver failure. Identification and improvement of precipitating aspects remain the foundation of treatment, and morbidity and mortality can be decreased by timely treatment. The medical diagnosis and management of HE in ED could be challenging and requires setup of care in seasoned centers with communication between ED physicians, hepatologists, and cosmetic surgeons. HE in cancer patients is multifactorial and needs specific therapy for HE as well as management of the underlying etiology.**

Keywords: emergency department (ED), pathogenesis, classification, diagnosis, treatment.

1. INTRODUCTION

Hepatic encephalopathy (HE) is a major and progressive but possibly reversible condition with a wide spectrum of neuropsychiatric abnormalities and motor disruptions that ranges from mild alteration of cognitive and motor function to coma and death [1]. It is a difficult problem of advanced liver illness where overt kinds are estimated to occur in 30% to 45% of patients with liver cirrhosis and in 10% to 50% of patients with transjugular intrahepatic portosystemic shunts [2].Minimal HE, which is characterized by more subtle motor and cognitive shortages, impacts roughly 20% to 60% of patients with liver illness. Cancer patients can be at risk for liver injury and HE due to numerous factors. The factors include preexisting liver illness, primary liver tumors, liver metastases of extrahepatic malignancies, compromised portal or hepatic venous circulation, hepatotoxicity because of chemotherapy, and bone marrow transplantation [3], [4].Due to distinctions in etiology and extent, and subtle findings in mild HE, the diagnosis and management of HE might be challenging for physicians.

This article aims to help with recognition and management of HE in the emergency department (ED) by reviewing its pathogenesis, classification, diagnosis, grading, and treatment.

2. METHODOLOGY

A comprehensive search was conducted through major databases; Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, through November, 2017. The search strategy used Mesh terms; encephalopathy, emergency department, management, we also searched references of potentially eligible articles were reviewed to identify all potentially eligible articles. and we limited our search in English language, and human trails only.

3. DISCUSSION

- **PATHOGENESIS:**

HE is a reversible metabolic encephalopathy related to variable degrees of mind edema. The pathogenesis is multifactorial and includes neurotoxicity of ammonia, oxidative stress, endogenous benzodiazepine-like ligands, astrocyte swelling, g-aminobutyric acid-- like particles, abnormal histamine and serotonin neurotransmission, endogenous opioids,

neurosteroids, inflammatory cytokines, and prospective manganese toxicity [4]. There is convincing evidence from animal and imaging research studies regarding the function of ammonia and cerebral edema as significant contributors to the advancement of HE [5].Cerebral edema is partially as a result of uptake of ammonia into astrocytes, where it is integrated with intracellular glutamate to generate glutamine, which causes cellular swelling. In patients with acute liver failing, higher uptake of ammonia in the brain, raised cerebral edema, and intracranial pressure (ICP) resulting in boosted mortality from cerebral herniation have been observed [6].

The ammonia theory does not completely explain the pathophysiology of HE because there are inconsistent changes in central nerve system functions when blood ammonia levels are raised. On the other hand, HE is induced more consistently by rising ammonia levels in the presence of inflammatory mediators [7].The accurate system underlying the synergism in between inflammatory mediators and ammonia remains unclear.

- **CLASSIFICATION:**

The World Congress of Gastroenterology has suggested three main categories of HE based on the underlying liver dysfunction (Box 1) [1].Type A HE is related to acute liver failing and progresses swiftly to seizures, decerebrate rigidity, coma, and regularly fatality. Types B and C are chronic problems and could manifest as minimal or overt HE. Overt HE can additionally be classified as episodic or persistent HE. Episodic HE is the more common kind of overt HE and provides with short durations of changes in consciousness over hrs to days. These periods are typically triggered by increased blood ammonia levels or intensifying liver illness. Patients with anecdotal HE usually go back to a normal psychological state with therapy and good supportive care. In consistent HE, despite fluctuating degrees of consciousness, patients do not return to a normal psychological state.

Box 1. Classification of HE.

1) Type A: HE associated with acute liver failure
2) Type B: HE associated with portosystemic bypass and no intrinsic liver disease
3)Type C: HE associated with cirrhosis and portal hypertension

- **DIAGNOSIS OF CHRONIC HEPATIC ENCEPHALOPATHY:**

Minimal HE is common in patients with cirrhosis, and it is characterized by regular neurologic findings and cognitive impairments that are noticeable just by psychometric examinations. Patients with minimal HE experience damaged psychomotor speed, visual understanding, focus and concentration, slow-moving mental processing, and memory loss. As a result of these alterations, patients commonly have difficulty with social communications and in doing their job, causing lowered health-related lifestyle [8] [9], [10], [11].The current meaning of very little HE is based on at the very least two psychometric tests. To fulfill the definition of HE, the results of each test need to be two basic deviations much less than normal. Regardless of their effectiveness and sensitivity, routine use these tests is challenged by copyright issues, need for psychological expertise for test analysis, and time should execute them. If psychometric tests are not available and medical suspicion of minimal HE is high, a test of empiric treatment with lactulose can be started [12].

Clinical symptoms, electroencephalography, neuroimaging, and blood ammonia screening are made use of for screening of patients for obvious HE. It is identified by alterations in mental condition and generalised motor disruption. Slow, monotonous speech and loss of fine motor skills are the hallmarks implicating the visibility of overt HE. The professional features of obvious HE are shown in Box 2 [13].Nevertheless, these indications are general and can be seen in other encephalopathies as well. The detection and differentiation of overt HE in cirrhotic patients has prognostic significance as these patients need to be evaluated for liver transplantation. The diagnosis of overt HE is based upon:

- known or suspected liver disease and/or portosystemic shunt,
- neurologic and/or cognitive impairment found by specific testing or clinical examination,
- exclusion of other encephalopathies,
- identification and resolution of all precipitating factors (Box 3)[14].

Box 2 Clinical features of overt HE

1) Slow, monotonous speech pattern
2) Loss of fine motor skills
3) Extrapyramidal type movement disorders
4) Hyperreflexia, Babinski sign, clonus
5) Asterixis
6) Hyperventilation
7) Seizures
8) Confusion, coma
9) Decerebrate/decorticate posturing

Grading of HE carries prognostic and therapeutic significance. West Haven Criteria (Box 4) and the Glasgow Coma Scale can be used to grade the intensity of HE [15]. Neuroimaging researches are typically carried out to eliminate other possible reasons of encephalopathy and to demonstrate the cerebral edema. Magnetic resonance imaging of brain is specifically helpful in diagnosing HE in patients with portosystemic shunts yet no intrinsic liver disease. As an outcome of decreased first-pass clearance of dietary manganese, these patients have accumulation of manganese in the basic ganglia. The accumulation of manganese is detected as hyperintensity of the basal ganglia on T1-weighted photos and indicates considerable portosystemic shunting [16].Blood ammonia degrees can associate with the seriousness of HE if determined suitably [17].The proper method is to place the specimen on ice and perform the assay within 30 mins of drawing blood. Failing to do so and executing the assay on postprandial blood will certainly lead to artificial elevations. High ammonia levels in a comatose patient could be due to cirrhosis, a urea cycle disorder, or seizure activity. Ammonia degrees in each stage of overt HE overlap widely; as a result, no constant relationship exists in between venous ammonia degrees and risk for cerebral edema in patients with cirrhosis [7].

Box 3. Precipitating factors for HE

1) Increased nitrogen load	**3) Drugs**
Gastrointestinal bleeding	Narcotics, tranquilizers, sedatives
Excess dietary protein	**4) Miscellaneous**
Azotemia	Infection
Constipation	Surgery
2) Electrolyte imbalance	Superimposed acute liver disease
Hyponatremia	Progressive liver disease
Hypokalemia	Transjugular intrahepatic portosystemic shunt
Metabolic alkalosis/acidosis	
Hypoxia	
Hypovolemia	

Box 4. West Haven criteria for grading hepatic encephalopathy

Grade 0	**Grade 3**
Lack of detectable changes in personality or behavior	Somnolence, confusion, disorientation to place, bizarre behavior, clonus, nystagmus, positive
No asterixis	Babinski sign
Grade 1	Asterixis usually absent
Trivial lack of awareness, shortened attention span, sleep disturbance, and altered mood	**Grade 4**
Asterixis may be present	Coma and lack of verbal, eye, and oral response
Grade 2	
Lethargy, disorientation to time, amnesia of recent events, impaired simple computations, inappropriate behavior, slurred speech	
Asterixis is present	

- **HEPATIC ENCEPHALOPATHY IN ACUTE LIVER FAILURE:**

HE has prognostic relevance in acute liver failing. Amongst 136 patients from the United States Acute Liver Failure Study, 31% with mild HE either went through liver transplantation or died [18].Liver transplantation or death happened in 74% of 217 patients with severe HE in the United Kingdom [19].Brain edema and intracranial hypertension (ICH) are severe consequences of extreme HE in acute liver failing. The threat of edema is extremely low in quality 1 and 2 HE, however raises to 25% to 35% in quality 3 HE and to 65% to 75% or greater in grade 4 HE [20].Ammonia, infection/inflammation, and hyponatremia are the primary factors to the advancement of brain edema in acute liver failing. Higher arterial ammonia levels were discovered to be predictive of higher mortality and are associated with even more complications including cerebral edema, seizures, and ventilation demand [6].Among patients with quality 3 and 4 HE, arterial ammonia values above 200 mmol/L were found to be practically usually associated with cerebral uncal herniation, and levels listed below 150 mmol/L showed up to be safety [21].Venous ammonia levels are less informative because of large arteriovenous variant of ammonia in acute liver failing. When ammonia concentration can not be lowered with conventional treatments, continuous venovenous hemofiltration might be utilized to reduce arterial ammonia concentration dramatically. Infection/ inflammation have been shown to be related to advancement and development of HE in acute liver failing [22].Roughly 25% of patients with acute liver failing have hyponatremia, which is more noticeable in those with severe encephalopathy [6].The pathogenesis of hyponatremia in acute liver failing continues to be uncertain, however quantity overload and vasopressin secretion are thought to be contributing factors. In patients with acute liver failing, decerebrate posturing, pupillary modifications, and oculovestibular response abnormalities all suggest boosted ICP. Unfortunately, the sensitivity of imaging research studies with respect to information concerning brain edema in acute liver failing is low. Invasive surveillance is the most precise device to gauge ICP; nevertheless, intracranial blood loss in the setup of coagulopathy stays a significant complication. The frequency of bleeding ranges between 10% and 22% [23]. Aggressive modification of coagulation parameters, with the addition of recombinant factor VIIa, might decrease the threat of bleeding.

- **MANAGEMENT OF HEPATIC ENCEPHALOPATHY IN ACUTE LIVER FAILURE:**

It is preferable to follow patients with acute liver failing and grade 1 HE in the intensive care unit. Nevertheless, they can likewise be admitted to a medicine ward with skilled nursing care and frequent neurologic monitoring. A quiet environment is preferred to prevent agitation. Patients with grade 2 HE must be admitted to intensive care units. Sedation must be avoided if possible. Small dosages of short-acting benzodiazepines could be utilized if needed. Going imaging is handy to exclude various other possible reasons for encephalopathy. Patients with grade 2 HE could be treated with lactulose to lower ammonia levels. Data from the United States Acute Liver Failure Study Group recommend that lactulose use is associated with a tiny rise in survival however no difference in intensity of HE or total result [24].Patients with grade 3 and 4 HE need intubation for airway protection. Short-acting representatives such as propofol are preferred for sedation. Identification of early cerebral edema at this phase is essential as brain perfusion should be maintained and herniation prevented up until transplantation. Clinical symptoms of raised ICP such as hypertension, bradycardia, and uneven respiration might not be present at this phase. Therefore, ICP monitoring tools are useful in recognizing very early analytical edema. These devices can reveal altitudes in ICP and reductions in cerebral perfusion pressure (CPP). ICP must be maintained below 20 to 25 mm Hg with CPP above 50 to 60 mm Hg [25].Prolonged ICP greater than 40 mm Hg and CPP much less than 50 mm Hg have been revealed to be associated with bad end result [26].Refractory ICH and reduced CPP are contraindications for liver transplantation. Clinical trials have shown that control of elevated ICP enhances survival [26].Mannitol is effective in the short-term to lower cerebral edema. It is provided as an IV bolus of 0.5 to 1 g/kg. The dosage could be repeated when or twice. Hypertonic saline to induce hypernatremia (150 mmol/L) might be made use of to control ICH based upon information from patients with head injury. Two studies revealed significant improvement in ICP and CPP after hypernatremia was generated with 3% saline in pediatric patients with head trauma and resistant ICH [27]. Moderate hypernatremia has likewise been revealed to lower ICP in patients with acute liver failure. In one study, 30% hypertonic saline was offered to patients with acute liver failing and quality 3 or 4 HE [28].The infusion rate was titrated in between 5 and 20 mL/h to preserve serum salt levels at 145 to 155 mmol/L. The authors wrapped up that patients with hypernatremia had significantly lower ICP and reduced occurrence of scientifically significant ICH. However, since hypertonic saline options are connected with really high salt lots, caution is suggested, particularly for patients with kidney dysfunction. Undoubtedly, mostpatients because study obtained constant venovenous hemofiltration, which buffered salt overload.

Hyperventilation to decrease PaCO2 to 25 to 30 mm Hg could be borrowed if ICH can not be regulated with mannitol or other steps in patients with acute liver failure. Nonetheless, both mannitol and hyperventilation are not advised for routine or prophylactic use. Although controlled trials are doing not have, some centers prefer to keep the core temperature at 36C in those intubated for HE and at 34C in those developing ICH [29].Patients with acute liver failure and dynamic HE are taken into consideration as possibly infected and need to be begun on empiric antibiotics [30]. Most patients with acute liver failing need renal replacement therapy, which is more reliable in preventing brain edema instead of treating it. Intravenous management of N-acetylcysteine has been reported to boost survival dramatically in patients with acute liver failing and mild HE [31].Nevertheless, there was no effect on survival of patients with extreme HE. Acute liver failing is an uncommon problem; few regulated tests exist for its treatment, and criteria of care have not been developed. The recommended management of HE in acute liver failure, based upon professional viewpoints and data from limited research studies, is summarized in Box 5 [32].

Box 5. Management of cerebral edema and intracranial hypertension in acute liver failure [32].

Grade 1 and 2 encephalopathy :	**Grade 2 and 3 encephalopathy:**
Consider transfer to liver transplant facility	Continue management as above
Perform head imaging to rule out other causes of alterations in mental status	Intubate trachea
Avoid stimulation	Elevate head at 30
Avoid sedation if possible	Consider placing ICP monitoring device
Antibiotics: survey and treat infection, prophylaxis possibly helpful	Treat seizures (phenytoin)
Lactulose possibly helpful	Mannitol for severe elevation of ICP or first clinical signs of herniation
	Hyperventilation may be used for impending herniation

4. CONCLUSION

HE is a typical and significant complication of chronic or acute liver failure. Identification and improvement of precipitating aspects remain the foundation of treatment, and morbidity and mortality can be decreased by timely treatment. The medical diagnosis and management of HE in ED could be challenging and requires setup of care in seasoned centers with communication between ED physicians, hepatologists, and cosmetic surgeons. HE in cancer patients is multifactorial and needs specific therapy for HE as well as management of the underlying etiology.

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