

Hepatic Encephalopathy: Diagnosis and Current Therapies

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Abstract: Hepatic encephalopathy (HE) is a neuropsychological, and a serious neurotoxic disease. HE varies in clinical presentation, in pathogenesis and treatment. HE is caused by the accumulation in the bloodstream of toxic substances that are normally removed by the liver. Clinical manifestations of HE include a wide spectrum of neuropsychiatric and neurological symptoms, disorientation and poor coordination. Acute HE is associated with severe liver failure in patients with fulminant hepatic failure. In chronic HE have neuropsychiatric syndrome characterized with depression of the central nervous system, with varying degrees of severity. HE is traditionally graded into four clinical stages. The synergistic effects of excess ammonia and inflammation cause astrocyte swelling and cerebral edema. Diagnosis of HE include neuropsychometric tests, brain imaging and clinical scales, the West Haven Criteria. Treatment is based on reducing the production and absorption of ammonia, with anti-microbial agent as rifaximin, and lactulose with probiotics added.

Keywords: Hepatic encephalopathy, Diagnosis, Management, and Therapy.

I. Introduction

Hepatic encephalopathy (HE) is a neurocognitive disorder that is associated with both acute and chronic liver injury. It has grown to become a dynamic syndrome, spanning a spectrum of neuropsychological impairment from normal performance through coma [1]. HE occurs in patients with acute or chronic liver disease and encompasses numerous neuropsychiatric disturbances. Various hepatic disorders can give rise to different types of liver - related encephalopathy. These diverse encephalopathy syndromes vary in prevalence, in laboratory and clinical manifestations, in pathogenesis, in hepatic histology and in treatment [2]. Individuals with cirrhosis, the risk of developing hepatic encephalopathy is 20% per year, and at any time about 30-45 % of people with cirrhosis exhibit evidence of covert encephalopathy. The prevalence of minimal hepatic encephalopathy detectable on formal neuropsychological testing is 60 -80%; this increases the likelihood of developing overt encephalopathy in the future [3]. HE is caused by the accumulation in the bloodstream of toxic substances that are normally removed by the liver [4]. Acute HE is associated with severe acute liver failure and occurs in patients with fulminant hepatic failure (FHF) [2]. FHF is the consequence of hepatic impairment, including failure to remove ammonia from the portal blood or failure to provide excitatory central nervous system stimulation. The blood brain barrier usually is injured in FHF [5]. Chronic HE is a complex neuropsychiatric syndrome characterized by depression of the central nervous system, and can occur with varying degrees of severity [5]. Clinical picture of HE encompasses a wide spectrum of neuropsychiatric and neurological symptoms. HE is traditionally graded into four clinical stages of severity [5]. Symptoms of HE can include confusion, disorientation and poor coordination. A general consensus exists that synergistic effects of excess ammonia and inflammation cause astrocyte swelling and cerebral edema; however the precise molecular mechanisms that lead to these morphological changes in the brain are unclear [6]. Diagnosis of HE include neuropsychometric tests, brain imaging and clinical scales (such as the West Haven criteria) [6]. Empiric therapy for HE is largely based on the principle of reducing the production and absorption of ammonia in the gut through administration of pharmacological agents such as rifaximin and lactulose [6]. The paper reviews the diagnosis and current therapies of hepatic encephalopathy.

II. History

The occurrence of disturbed behavior in people with jaundice may have been described in antiquity by Hippocrates of Cos (ca. 460-370 BCE) [7,8]. Celsus and Galen (first and third century respectively) both recognized the condition. Many modern descriptions of the link between liver disease and neuropsychiatric symptoms were made in the eighteenth and nineteenth century, for instance, Giovanni Battista Morgagni (1682-1771) reported in 1761 that it was a progressive condition [8]. In the 1950s, several reports enumerated the numerous abnormalities reported previously, and confirmed the previously enunciated theory that metabolic impairment and portosystemic shunting are the underlying mechanism behind hepatic encephalopathy, and the nitrogen-rich compounds originate from the intestine [7,9]. Many of these studies were done by Professor Dame

Sheila Sherlock(1918-2001),then at the Royal Postgraduate Medical School in London and subsequently at the Royal Free Hospital. The same group investigated protein restriction[8],and neomycin [10].The West Haven classification was formulated by Prof Harold Conn(1925-2011) and colleagues at Yale University while investigating the therapeutic efficacy of lactulose[11].

III. Contributory Factors And Grading

HE is caused directly by liver failure; this is more likely in acute liver failure. More commonly, especially in chronic liver disease, hepatic encephalopathy is caused or aggravated by an additional cause, and identifying these causes can be important to treat the episode effectively[12].Frequent contributory factors or causes include[12,4,13].

- a) **Excessive nitrogen** load due to consumption of large amounts of proteins, gastrointestinal bleeding, failure to excrete nitrogen containing waste-urea, and constipation.
- b) **Electrolyte** or metabolic disturbance-Hyponatremia
- c) **Drugs** and medications-sedative i.e.,benzodiazepine,narcotics,sedativeantipsychotics,and alcohol intoxication.
- d) **Infection**-pneumonia, urinary tract infection,spontaneous bacterial peritonitis, and other infections.
- e) **Miscellaneous**-Surgery, progression of liver disease, liver damage, alcoholichepatitis, and hepatitis A.Unknown causes include 20% to 30 % cases, no clear cause for attack can be found.

HE may also occur after the creation of a trans jugular intrahepatic portosystemic shunt (TIPS).This is used in the treatment of refractory ascites, bleeding from esophageal varices and hepatorenal syndrome [14,15].TIPS-related encephalopathy occurs in about 30% of cases, with the risk being higher in those with previous episodes of encephalopathy, higher age, female sex and liver disease due to causes other than alcohol[13].

Grading.The severity of hepatic encephalopathy is graded with the West Haven Criteria; this is based on the level of important autonomy, changes in consciousness, intellectual function, behavior, and the dependence on therapy[12,16],include: Grade 1-Trivial lack of awareness; euphoria or anxiety; shortened attention span, impaired performance of addition or subtraction.Grade2-Lethargy or apathy, minimal disorientation for time or place, subtle personality change; inappropriate behavior. Grade 3-Somnolence to semi stupor, but responsive to verbal stimuli;confusion, gross disorientation and Grade 4-Coma(unresponsive to verbal or noxious stimuli).

Classification of HE was introduced at the World Congress of Gastroenterology,1998 in Vienna. According to this classification, HE is subdivided in type A,B,and C depending on the underlying cause[16].**Type A-acute** describes HE associated with acute liver failure, typically associated with cerebral edema, **Type- B-bypass** is caused by portal-systemic shunting without associated intrinsic liver disease. **Type C-cirrhosis** occurs in patients with cirrhosis-this type is subdivided in **episodic** and minimal encephalopathy. The term minimal encephalopathy(MHE) is defined as encephalopathy that does not lead to clinically overt cognitive dysfunction, but can be demonstrated with neuropsychological studies[16,17].This is still an important finding, as minimal encephalopathy has been demonstrated to impair quality of life and increase risk of involvement in in road traffic accidents[9].

IV. Pathophysiology

Elevated blood ammonia concentrations are common in portal-systemic encephalopathy (PSE)[2,5].However, blood ammonia does not necessarily correlates with a patient's syndromes or neuropsychiatric status[5].Ammonia intoxication directly or indirectly is responsible for most episodes of HE. The precise neurochemical mechanisms underlying the pathogenesis of HE remains unknown. One explanation of HE is ammonia induced primary gliopathy,leading to impaired neuronal function[18].Elevation of cerebrospinal fluid glutamine concentration,which effects nitrogenous intoxication, is also specific for PSE and shows a reliable correlation with HE severity[19,].

There are various explanations why liver dysfunction or portosystemic shunting lead to encephalopathy. In healthy subjects,nitrogen-containing compounds from the intestine,generated by gut bacteria from food, are transported by the portal vein to liver, where 80-90% is metabolized through the urea cycle and/or excreted immediately. This process is impaired in all subtypes of HE, either because the hepatocytes (liver cells) are incapable of metabolizing the waste products or because portal venous blood bypasses the liver through collateral circulation or a medically constructed shunt. Nitrogenous waste products accumulate in the systemic circulation(hence the older term "portosystemic encephalopathy(PSE).The most important waste product is ammonia(NH₃).This small molecule crosses the blood-brain barrier and is absorbed and metabolized

by the astrocytes, a population of cells in the brain that constitutes 30% of cerebral cortex. Astrocytes use ammonia when synthesizing glutamine from glutamate. The increased levels of glutamine lead to an increase in osmotic pressure in the astrocytes, which become swollen. There is increased activity of the inhibitory γ -aminobutyric acid (GABA) system, and the energy supply to other brain cells is decreased. This can be brought of as an example brain edema of the “cytotoxic” type [1].

Despite numerous studies demonstrating the central role of ammonia, ammonia levels don't always correlate with severity of the encephalopathy; it is suspected that this means that more ammonia has already been absorbed into the brain in those with severe symptoms whose serum levels are relatively low [12,4]. Other waste products implicated in HE include mercaptans (substances containing a thiol group) short-chain acids and phenol [4]. Numerous other abnormalities have been described in HE, although their relative contribution to the disease state is uncertain. Loss of glutamate transporter gene expression (especially EAAT 2) has been attributed to acute liver failure [20]. Benzodiazepine-like compounds have been detected at increased levels as abnormalities in the GABA neurotransmission system. An imbalance between aromatic amino acids (phenylalanine, tryptophan and tyrosine) and branched-chain amino acids (leucine, isoleucine, and valine) has been described; this would lead to the generation of false neurotransmitters (such as octopamine and 2-hydroxyphenethylamine). Dysregulation of the serotonin system, too, has been reported. Depletion of zinc and accumulation of manganese may play a role [12,4]. Inflammation elsewhere in the body may precipitate encephalopathy through action of cytokines and bacterial lipopolysaccharide on astrocytes [13]. The central role of ammonia in the pathogenesis of HE remains incontrovertible. However, over the past 10 years, the HE community has begun to characterize the key roles of inflammation, infection, and oxidative/nitrosative stress in modulating the pathophysiological effects of ammonia on the astrocyte [21].

V. Clinical Manifestations

Clinical picture of HE encompasses a wide spectrum neuropsychiatric and neurological symptoms. HE traditionally is graded into four clinical stages of severity ranging from changes in personality and memory disturbances (grade 1) to deep coma (grade IV) [2,5]. Degree assessment of encephalopathy is based on the temporal relation of consciousness, intellectual function, personality-behavior, neuromuscular abnormalities, metabolic slowing of electroencephalogram (EEG) and elevated blood ammonia concentrations [2,22]. HE is often latent and subclinical, and in patients with normal mental state and EEGs can be detected only by psychometric testing and evoked potentials [23,24].

Acute HE is associated with severe acute liver failure and occurs in patients with fulminant hepatic failure (FHF) [2,25]. FHF is the consequence of hepatic impairment including failure to remove ammonia from the portal blood or to provide excitatory central nervous system stimulation. The Blood-brain barrier usually is injured in FHF [5,26].

Chronic HE is a complex neuropsychiatric syndrome characterized by depression of the central nervous system, and can occur with varying degrees of severity [5]. The most common type of HE is portal-systemic encephalopathy (PSE), which occurs almost exclusively in patients with cirrhosis [2,27]. PSE is characterized by elevated arterial ammonia concentrations and initiated by increased concentrations of ammoniagenic substrates. Pseudo-PSE (PsPSE), the second most prevalent type of HE, is the result of central nervous system depression by non-nitrogenous neurotransmitter analytes. Patients with this disorder characteristically have a normal blood ammonia concentration.

Other researchers contend that the mildest form of HE is difficult to detect clinically, but may be demonstrated on neuropsychological testing. It is experienced as forgetfulness, mild confusion, and irritability. The first stage of HE is characterized by an inverted sleep-wake pattern (sleeping by day, being awake at night). The second stage is marked by lethargy and personality changes. The third stage is marked by worsened confusion. The fourth stage is marked by a progression to coma [12].

More severe forms of HE lead to a worsening level of consciousness, from lethargy to somnolence and eventually coma. In the intermediate stages, characteristic jerking movement of limbs is observed (asterixis, “liver flap” due to its flapping character); this disappears as somnolence worsens. There is disorientation and amnesia, and uninhibited behavior may occur. In the third stage, neurological examination may reveal clonus and positive Babinski sign. Coma and seizures represent the most advanced stage; cerebral edema (swelling of the brain tissue) leads to death [12].

HE often occurs together with other symptoms and signs of liver failure. These may include jaundice (yellow coloration of skin and whites of the eyes), ascites (fluid accumulation in the abdominal cavity), and peripheral edema (swelling of the legs due to fluid build-up in the skin). The tendon reflexes may be exaggerated, and the plantar reflex may be abnormal, namely extending rather than flexing (*Babinski's* sign) in severe HE. A particular smell (*foetor hepaticus*) may be detected [4].

VI. Diagnosis

Diagnosis of HE can only be made in the presence of confirmed liver disease (type A and C) or a portosystemic shunt (type B), as its symptoms are similar to those encountered in other encephalopathies. To make the distinction, abnormal liver function tests and/or ultrasound suggesting liver disease are required, and ideally liver biopsy[12,4].The symptoms of HE may also arise from other conditions, such as cerebral hemorrhage and seizures(both of which are more common in chronic liver disease)A CT scan of the brain may be required to exclude hemorrhage, and if seizure activity is suspected an electroencephalogram(EEG) study may be performed[12].Rare mimics of the encephalopathy are meningitis, encephalitis, Wernick's encephalopathy and Wilson's disease, these may be suspected on clinical grounds and confirmed with investigations[4,16].

The diagnosis of HE is a clinical one, once other causes for confusion or coma have been excluded; no test fully diagnoses or excludes it.Serum ammonia levels are elevated in 90% pf patients, but not at all hyperammonemia(high ammonia level) is associated with encephalopathy[12,4]. A CT scan of the brain usually shows no abnormality except in stage IV encephalopathy, when cerebral edema may be visible[4].Other neuroimaging modalities, such as magnetic resonance imaging (MRI),are not currently regarded as useful, although they may show abnormalities[16]. Electroencephalogram shows no clear abnormalities in stage 0,even if minimal HE is present; instages I,II, and III there are triphasic waves over the frontal lobes that oscillate at 5 Hz, and stage IV there is slow delta wave activity[12].However, the changes in EEG are not typical enough to be useful in distinguishing hepatic encephalopathy from other conditions[16].

Once the diagnosis of HE has been made, efforts are made to exclude underlying causes. This requires blood tests (urea and electrolytes, full blood count, liver function test),usually a chest X-rays, and urinalysis. If there is ascites, diagnostic paracentesis (removal of fluid sample with a needle) may be required to identify spontaneous bacterial peritonitis (SBP)[12].

The diagnosis of minimal HE requires neuropsychological testing by definition.Older tests include "numbers counting test" A and B (measuring the speed at which one could connect randomly dispersed numbers 1-20),the "block design test"[16].In 2009 an expert panel concluded that neuropsychological test batteries aimed at measuring multiple domains of cognitive function are generally more reliable than single tests, and tend to be more strongly correlated with functional status. Both the Repeatable Battery for Assessment of Neuropsychological Status((RBANS) and PSE-syndrome test[28,7] may be used for this purpose[17].The PSE-syndrome test developed in Germany and validated in several other European countries, incorporates older assessment tools such as the number connection test[16,17,3,7].

VII. Therapy

Those with severe encephalopathy (stages 3 and 4) are at risk of obstructing their airways due to decreased reflexes such as gag reflex. This can lead to respiratory arrest. Transferring the patient to higher level of nursing care, such as an intensive care unit, is required and intubation of the airway is often necessary to prevent life-threatening complications (e.g.,aspiration or respiratory failure)[4,29,].Placement of a nasogastric tube permits the safe administration of nutrients and medications[12].The treatment of encephalopathy depends on the suspected underlying cause(type A,B,or C) and the presence of or absence of underlying causes. If encephalopathy develops in acute liver failure(Type A),even in a mild form(grade 1-2),it indicates that liver transplant may be required, and transfer to a specialist center is advised[28].HE type B may arise in those who have undergone a TIPSS procedure; in most cases this resolves spontaneously or with the medical treatments, but in small proportion of about 5%,occlusion of the shunt is required to address the symptoms[13].In HE type C,the identification and treatment of alternative or underlying causes is central to the initial management[12,4,13,3].Given the frequency infections as the underlying cause, antibiotics are often administered empirically[12,13].Once an episode of encephalopathy has been effectively treated, a decision may need to be made on whether to prepare for liver transplant[3]

Protein restricted diet.Dietary restrictions of protein are often a first-line treatment for HE, but little evidence exists to support it efficacy in symptomatic hepatic encephalopathy patients. Direct restriction alone cannot be the sole treatment [30].Some experts prescribe diet modifications that include protein intake restriction to 20 or more grams per day during acute HE exacerbations. Continuing protein restrictions are no longer fully supported because there is a risk of initiating catabolic processes that will also increase ammonia levels [31].Furthermore, many people with chronic liver disease are malnourished and require protein to maintain a stable body weight. A diet with adequate protein and energy is therefore recommended [12,13].

Probiotics.In addition to limiting protein intake that normal intestinal flora breaks down into ammonia; probiotics may be prescribed to support intestinal bacteria that are less likely to create these by products. Multiple studies have shown some benefit of probiotics for minimalHE,as well as other conditions affecting

bowel function, such as lactose intolerance, irritable bowel syndrome, and colitis.[32,33,34].Studies of the effectiveness of probiotics to lower ammonia levels compared with other treatments such as disaccharides have been promising. Consensus does not exist as to which microbes are most effective for lowering ammonia levels in patients with HE, but a systematic review of available studies is under way[32,33].

Latulose/latito-disaccharides. Latulose and latitol are disaccharides that are not absorbed from the digestive tract. They are thought to decrease the generation of ammonia by bacteria, render the ammonia inabsorbable by converting to ammonium (NH₄), and increase transit of bowel content through gut. Doses of 15-30 ml are administered three times a day; the result is aimed to be 3- 5 stools a day, or (in some setting) a stool pH of <6.0[12,2,13,3]. Other theories of its action are the promotion of beneficial bacteria growth and inhibition of ammonia producing bacteria[35,36]. Lactulose may also be given by enema, especially if encephalopathy is severe[3]. More commonly, phosphate enemas are used. This may relieve constipation, one of the causes of encephalopathy, and increase bowel transit [12].

Antimicrobial agents. Antimicrobials, neomycin and metronidazole (also vancomycin, paromycin, and oral quinolones) were previously used as a treatment for HE. The rationale of their use was the fact that ammonia and other waste products are generated and converted by intestinal bacteria, and killing these bacteria would reduce the generation of these waste products. Neomycin was chosen because of its low intestinal absorption and similar aminoglycoside antibiotics may cause ototoxicity, nephrotoxicity if used parenterally. Later studies showed that neomycin was indeed absorbed eternally, with resultant complications. Metronidazole, similarly, was abandoned because prolonged use could cause peripheral neuropathy (nerve damage), in addition to gastrointestinal side effects[12]. A safer and probably more effective antibiotic is rifaximin, (37) a nonabsorbable antibiotic from the rifaximin class. This thought to work in a similar way, but without the complications attached to neomycin and metronidazole. The use of rifaximin is supported by better evidence than lactulose[18]. Rifaximin is absorbed from the intestinal tract with less than 0.2% found in the liver or kidney, compared to other antibiotics and excreted unchanged in feces[37]. Due to the long history and lower cost of lactulose use, rifaximin is only used as second-line treatment if lactulose is poorly tolerated or not effective. When rifaximin is added to lactulose, the combination of the two may be more effective than each component separately[12]. Rifaximin is more expensive than lactulose, but cost may be offset by reduced hospital admissions for encephalopathy[3].

The treatment of HE is aimed at reducing the absorption of potentially neurotoxic material from the gastrointestinal tract. This is achieved through dietary alteration as well as the use of agents which alter the nature and metabolism of the intestinal flora [38].

Prognosis. Once HE has developed; the prognosis is determined largely by other markers of liver failure, such as the levels of albumin, the prothrombin time, and the presence of ascites and level of bilirubin. Together with severity of encephalopathy, these markers have been incorporated into Child-Pugh score; this score determines the one- and two-year survival and may assist in decision to offer liver transplantation[16]. Min WC recommend the use of artificial liver to people on the waiting list of liver transplant or patients with hepatic insufficiency[39]. Xing and colleagues recommend the use of a 10-mm stent may be more effective than 8-mm or 12-mm stent for the selection of a TIPS stent for management of portal hypertension in liver cirrhosis [40]. In acute liver failure, the development of severe encephalopathy strongly predicts short-term mortality, and is almost as important as the nature of the underlying cause of liver failure in determining the prognosis. Historically, widely used criteria for offering liver transplantation, such as King's College Criteria, are of limited use and recent guidelines discourage excessive reliance on these criteria. The occurrence of HE in patients with Wilson's disease (hereditary copper accumulation) and mushroom poisoning indicates an urgent need for a liver transplant [29].

VIII. Conclusion

The therapy of hepatic encephalopathy is aimed to reduce production and absorption of neurotoxic-ammonia from the gastrointestinal tract. This can be achieved through dietary alteration, the use of rifaximin, lactulose, and probiotics which will alter the nature and metabolism of intestinal flora.

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