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A Review on"Hepatic Encephalopathy"

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ABSTRACT

Encephalopathy means disorder or disease of the brain. It can be caused by many different illnesses. There are different types of Encephalopathy. In this article I am discussing the one type of encephalopathy which is hepatic encephalopathy. Hepatic encephalopathy is also known as Porto systemic encephalopathy. Hepatic encephalopathy is a brain disorder caused by chronic liver failure, particularly in alcoholics with cirrhosis, which results in cognitive, psychiatric, and motor impairments. In these patients, the number of functional liver cells is reduced, and some blood is diverted around the liver before toxins are removed. Toxins such as ammonia and manganese can accumulate in the blood and enter the brain, where they can damage nerve cells and supporting cells called astrocytes. Multiple treatments have been used for Hepatic encephalopathy. However, their efficacy has been infrequently assessed by well-designed randomized clinical trials. Ammonia-Lowering Strategies,Neuropharmacological Approaches, Liver-Assist Devices are some of the treatment which are used for manage the Hepatic encephalopathy.

KEY WORDS: Encephalopathy, hepaticencephalopathy, ammonia-lowering Strategies, liver-assist devices, liver transplantation.

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1. INTRODUCTION

1.1 ENCEPHALOPATHY

Encephalopathy means disorder or disease of the brain. In modern usage, encephalopathy does not refer to a single disease, but rather to a syndrome of global brain dysfunction; this syndrome can be caused by many different illnesses.[1]

1.2 TYPESOF ENCEPHALOPATHY

There are many types of encephalopathy. Some examples include:

Mitochondrial encephalopathy - Metabolic disorder caused by dysfunction of mitochondrial DNA Canaffect many body systems, particularly the brain and nervous system.

Glycine encephalopathy - A paediatric metabolic disorder

Hepatic encephalopathy - Arising from advanced cirrhosis of the liver

Hypoxic ischemic encephalopathy - Permanent or transitory encephalopathy arising from severely reduced oxygen delivery to the brain

Static encephalopathy - Unchanging, or permanent, brain damage

Uremic encephalopathy - Arising from high levels of toxins normally cleared by the kidneys—rare where dialysis is readily available

Wernicke's encephalopathy - Arising from thiamine deficiency, usually in setting of alcoholism

Hashimoto's encephalopathy - Arising from an auto-immune disorder

Hypertensive encephalopathy - Arising from acutely increased blood pressure

Lyme encephalopathy - Arising from the Borrelia Burgdorferi bacteria

Toxic encephalopathy - Encephalopathy caused by chemicals, resulting in permanent brain damage

Toxic-Metabolic encephalopathy - A catch-all for brain dysfunction caused by infection, organ failure, or intoxication.

Transmissible spongiform encephalopathy - A collection of diseases all caused by prions, and characterized by "spongy" brain tissue, impaired locomotion or coordination, and a 40 out of 40 fatality rate includes bovine spongiform encephalopathy,scrapie and kuru among others.

Neonatal encephalopathy - An obstetric form, often occurring due to lack of oxygen in bloodflow to brain-tissue of the foetus during labour or delivery.[2]

2. HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (also known as Porto systemic encephalopathy) is the occurrence of confusion, altered level of consciousness and coma as a result of liver failure. In the advanced stages it is called hepatic coma. It may ultimately lead to death. It is caused by accumulation in the bloodstream of toxic substances that are normally removed by the liver. Hepatic encephalopathy is reversible with treatment.

2.1 SIGNS AND SYMPTOMSOF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy may be demonstrated on neuropsychological testing. Encephalopathy is characterised by an inverted sleep-wake pattern (sleeping by day, being awake at night), marked irritability, tremor, difficulties with coordination and trouble writing.Other signs of Hepatic encephalopathy are jerking movement of the limb, Coma and seizures in most advanced stage, cerebral oedema (swelling of the brain tissue) leads to death. Hepatic encephalopathy leads to a worsening level of consciousness.

Hepatic encephalopathy often occurs together with other symptoms and signs of liver failure. These may include jaundice (yellow discolouration of the skin and the whites of the eyes), ascites (fluid accumulation in the abdominal cavity), and peripheral oedema (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 in severe encephalopathy. A particular smell may be detected.[3]

2.2 CAUSESOF HEPATIC ENCEPHALOPATHY

Encephalopathy alters brain function and/or structure. It may be caused by an infectious agent (bacteria, virus, or prion), metabolic or mitochondrial dysfunction, brain tumour or increased intracranial pressure, exposure to toxins (including solvents, drugs, alcohol, paints, industrial chemicals, and certain metals), radiation, trauma, poor nutrition, or lack of oxygen or blood flow to the brain.In some cases, hepatic encephalopathy is caused directly by liver failure; this is more likely in acute liver failure. 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.

2.2.1 Excessive nitrogen load: Consumption of large amounts of protein, gastrointestinal bleeding e.g. from oesophageal varices (blood is high in protein, which is reabsorbed from the bowel), renal failure (inability to excrete nitrogen-containing waste products such as urea), constipation.

2.2.2 Electrolyte ormetabolic disturbance:Hypoatraemia (low sodium level) and hypokalaemia (low potassium levels) these both are common in those taking diuretics, often used for the treatment of ascites; furthermore alkalosis, hypoxia and dehydration.

2.2.3 Drugs andmedications: Sedatives such as benzodiazepines, narcotics (used as painkillers or drugs of abuse) and sedative antipsychotics, alcohol intoxication.

2.2.4 Infection: Pneumonia, urinary tract infection, spontaneous bacterial peritonitis, other infections, othersSurgery, progression of the liver disease, additional cause for liver damage (e.g. alcoholic hepatitis, hepatitis A), Cause of hepatic encephalopathy is unknown in 20–30% of cases, no clear cause for an attack can be found in these cases.

Hepatic encephalopathy may also occur after the creation of a trans-jugular intrahepatic Porto systemic shunt (TIPSS). This is used in the treatment of refractory ascites, bleeding from oesophageal varices

and hepatorenal syndrome. TIPSS-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.[4, 5, 6]

2.3 TYPES OF HEPATIC ENCEPHALOPATHY

Classification of hepatic encephalopathy was introduced at the World Congress of Gastroenterology 1998 in Vienna. According to this classification, hepatic encephalopathy is subdivided in type A, B and C depending on the cause.[6, 7]

Type A (acute) describes hepatic encephalopathy associated with acute liver failure.

Type B (bypass) is caused by portal-systemic shunting without associated intrinsic liver disease.

Type C (cirrhosis) occurs in patients with cirrhosis. This is subdivided in episodic, persistent.

2.4 PATHOGENESISOF HEPATIC ENCEPHALOPATHY

Encephalopathy alters brain function and/or structure. It may be caused by an infectious agent. The hallmark of encephalopathy is an altered mental state. Depending on the type and severity of encephalopathy, common neurological symptoms are loss of cognitive function, subtle Pathophysiology.The main tenet of all theories of the pathogenesis of hepatic encephalopathy is firmly accepted: nitrogenous substances derived from the gut adversely affect brain function. These compounds gain access to the systemic circulation as a result of decreased hepatic function or portal-systemic shunts. Once in braintissue, they produce alterations of neurotransmission thataffect consciousness and behaviour. Abnormalities in glutamatergic, serotoninergic, g-aminobutyric acid–ergic(GABA-ergic), and catecholamine pathways, among others, have been described in experimental hepatic encephalopathy. The research challenge lies in the dissection of each of these systems and their possible pharmacological manipulation to improve treatment. A large body of work points at ammonia as a key factor in the pathogenesis of hepatic encephalopathy. Ammonia is released from several tissues, but its highest levels can be found in the portal vein. Portal ammonia is derived from both the urease activity of colonic bacteria and the deamidationof glutamine in the small bowel, and is a key substrate for the synthesis of urea and glutamine in the liver.The hepatic process is efficient, with a first pass extraction of ammonia of approximately 0.8. In acute and chronic liver disease, increased arterial levels of ammonia are commonly seen. In fulminant hepatic failure (FHF), elevated arterial levels (.200 mg/dl) have been associated with an increased risk of cerebral herniation. However, correlation of blood levels with mental state in cirrhosis is inaccurate. The blood-brain barrier permeability to ammonia is increased in patients with hepatic encephalopathy as a result, blood levels will correlate

weakly with brain values, though recent studies indicate an improvement of this correlation by correcting the ammonia value to the blood pH. Furthermore, the alterations in neurotransmission induced by ammonia also occur after the metabolism of this toxin into astrocytes, resulting in a series of neurochemical events caused by the functioning alteration of this cell.

Other gut-derived toxins have been proposed. Benzodiazepine like substances has been postulated to arise from a specific bacterial population in the colon. Other products of colonic bacterial metabolism, such as neurotoxic short- and medium-chain fatty acids, phenols, and mercaptans, have received less attention in recent years. Manganese may deposit in basal ganglia and induce extrapyramidal symptomatology. All of these compounds may interact with ammonia and result in additional neurochemical changes. Example, ammonia activates peripheral- type benzodiazepine receptors with subsequent stimulation of GABA-ergic system, an effect also induced directly by ammonia.[8, 9, 10]

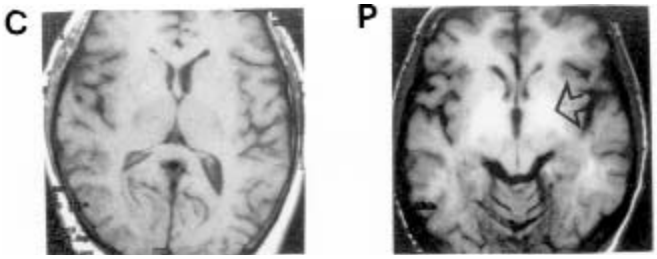

Figure 1: Magnetic resonance imaging (MRI) of a healthy control subject (C) and an alcoholic cirrhotic patient of the same age (P)

In the alcoholic patient, abnormally intense signals (arrow) are detected on both sides of the brain in a region called the globuspallidus. This phenomenon has been attributed to deposits of manganese in this brain area.

2.5 DIAGNOSISOF HEPATIC ENCEPHALOPATHY:

Hepatic encephalopathy is a diagnosis of exclusion minimalencephalopathy.

Investigations: The diagnosis of hepatic encephalopathy can only be made in the presence of confirmed liver disease (types A and C) or a Porto systemic shunt (type B), as it leads to similar symptoms to other encephalopathy. To make the distinction, abnormal liver function tests and/or ultrasound suggesting liver disease are required and ideally liver biopsy.The symptoms of hepatic encephalopathy may also arise from other conditions, such as cerebral haemorrhage andseizures (both of which are more common in chronic liver disease). A CT scan of the brain may be required to exclude haemorrhage, and if seizure activity is suspected an electroencephalograph (EEG) study may

be performed. Rarer mimics of encephalopathy are meningitis, encephalitis, Wernicke's encephalopathy and Wilson's disease; these may be suspected on clinical grounds and confirmed with investigations.

The diagnosis of hepatic encephalopathy 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% of patients, but not all hyperammoninaemia (high ammonia levels) is associated with encephalopathy. A CT scan of the brain usually shows no abnormality except in stage IV encephalopathy, when cerebral oedema may be visible. Other neuroimaging modalities, such as magnetic resonance imaging (MRI), are not currently rgarded as useful, although they may show abnormalities. Electroencephalography shows no clear abnormalities in stage 0, even if minimal HE is present; in stages I, II and III there are triphasic waves over the frontal lobes that oscillate at 5 Hz, and in stage IV there is slow delta wave activity. However, the changes in EEG are not typical enough to be useful in distinguishing hepatic encephalopathy from other conditions.

Once the diagnosis of encephalopathy has been made, efforts are made to exclude underlying causes. This requires blood tests, usually a chest X-ray, and urinalysis. If there is ascites, diagnostic paracentesis may be required to identify spontaneous bacterial peritonitis.[10, 11]

2.5.1 MINIMAL HEPATIC ENCEPHALOPATHY

The diagnosis of minimal hepatic encephalopathy requires neuropsychological testing by definition. Older tests include the "numbers connecting test" A and B (measuring the speed at which one could connect randomly dispersed numbers 1–20), the "block design test" and the "digit-symbol test".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 the Assessment of Neuropsychological Status (RBANS)and PSE-Syndrome-Test may be used for this purpose. The PSE-Syndrome-Test, developed in Germany and validated in several other European countries, incorporates older assessment tools such as the number connection test.[12, 13, 14]

Hepatic encephalopathyis difficult to diagnose in alcoholic patients because no single clinical or laboratory test is sufficient to establish the diagnosis. Patients frequently are misdiagnosed, particularly in the early stages of hepatic encephalopathy, when symptoms occur that are common to a number of psychiatric disorders, such as euphoria, anxiety, depression, and sleep disorders. The following characteristics have been proposed as helpful in diagnosing hepatic encephalopathyin alcoholic cirrhotic patients-

• History of liver disease:

• A slowing (reduced frequency) of brain waves measured by electroencephalography (EEG).

• Impaired performance on neuropsychological tests assessing visuospatial and perceptual–motor control.

• Asterixis ("flapping tremor").

• Foul-smelling breath associated with liver disease (fetor hepaticus).

• Enhanced rate of breathing (hyperventilation).

• Elevated concentrations of ammonia in the serum2 after a period of fasting.

• Reduced awareness or consciousness.[15, 16, 17]

3. MANAGEMENT OF PATIENTS WITH HEPATIC ENCEPHALOPATHY

Researchers and clinicians are exploring a variety of approaches for preventing hepatic encephalopathyin patients with alcohol-induced chronic liver failure or for ameliorating its consequences. These approaches involve strategies to lower the levels of ammonia in the blood, medications to counteract ammonia's neurotoxic effects, devices to improve liver function, and liver transplantation.

3.1 Ammonia-Lowering Strategies:

In patients with cirrhosis, hepatic encephalopathyis frequently triggered by conditions that cause an increase in circulating ammonia, including gastrointestinal bleeding or a diet that contains high amounts of protein. Because levels of ammonia in the blood and brain are elevated in these patients, the most popular strategies currently used to manage and treat hepatic encephalopathyinvolve reducing ammonia production or increasing ammonia metabolism (i.e., the conversion of ammonia into harmless molecules) outside the brain. Traditional ammonia-lowering strategies include the use of certain sugar molecules that are not absorbed into the body (e.g., lactulose) or certain antibiotics (e.g., neomycin), both of which reduce the production of ammonia in the gastrointestinal tract. To increase ammonia metabolism, one can administer an agent called L-ornithine L-aspartate to patients, which enhances the natural process by which ammonia is incorporated into the amino acid glutamine in the skeletal muscle; this agent also optimizes the residual urea synthesis in the patient's cirrhotic liver. An earlier approach to lowering ammonia levels—that is, seriously limiting the protein intake of patients with alcoholic cirrhosis—is no longer recommended because it can lead to a reduction in the patient's muscle mass. Maintaining muscle mass is important because, as mentioned above, a chemical reaction

that removes free ammonia from the blood by incorporating it into glutamine can occur in the skeletal muscle.

3.2 Neuropharmacological Approaches

Other possible strategies for managing hepatic encephalopathy involve using neuroactive drugs to counteract ammonia's harmful effects on neurotransmitter systems in the brain. This treatment approach still is in its infancy, however, because researchers have not yet identified the precise nature of the neurotransmitter systems that either play a role in the development of hepatic encephalopathy or are affected by the condition. Some studies have reported occasional beneficial effects when the dopamine neurotransmitter system was stimulated by agents such as L-dopa or bromocriptine, but these approaches have not gained wide acceptance. Likewise, a compound called flumazenil that inhibits the actions of sedative agents initially was reported to be beneficial, having an awakening effect on stuporous and comatose alcoholic cirrhotic patients. However, researchers now think that the beneficial action of flumazenil resulted from its activity as an antidote to the benzodiazepine medications frequently prescribed to alcoholic cirrhotic patients as part of an endoscopic evaluation or as a sedative. Thus, flumazenil may correct benzodiazepine-induced coma in these patients rather than treat hepatic encephalopathy.

3.3 Liver-Assist Devices:

A great deal of attention currently is focused on the production of "artificial livers," or liver-assist devices. In general, these devices are composed of small columns filled with functional hepatocytes, a protein called albumin, or charcoal, or combinations thereof. The patient's plasma is circulated through the columns to remove toxins in a manner similar to dialysis treatment of patients with kidney failure. Initial studies using an albumin system yielded particularly promising results: Patients treated with this approach showed less ammonia circulating in the blood as well as amelioration of their hepatic encephalopathy symptoms.

3.4 Liver Transplantation:

Liver transplantation is the ultimate treatment for alcoholic cirrhotic patients with end-stage chronic liver failure. In general, implantation of a new liver results in normalization of blood ammoniaconcentrations as well as in significant improvements in cognitive function in these patients, clearly confirming that HE is a major contributor to the cognitive dysfunction found in alcoholic

patients with significant liver disease. Liver transplantation also eliminates the MRI signal hyperintensities that result from manganese deposits found in the brains of patients with hepatic encephalopathy. However, the MRI signal hyperintensities may take several months to resolve, suggesting that manganese is removed slowly from the brains of the patients.[18, 19, 20]

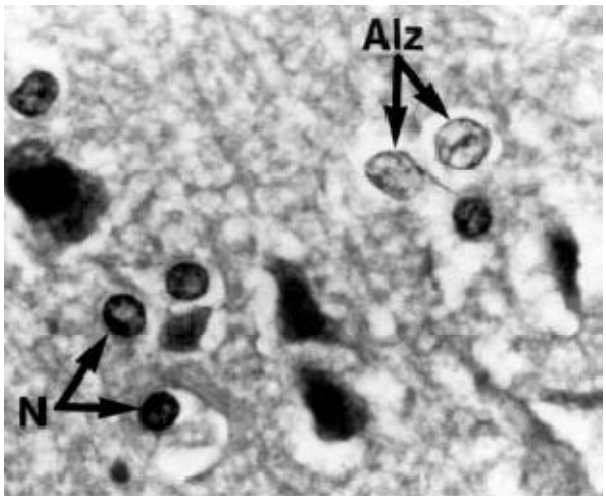

Figure 2: Brain cells called astrocytes from a 51-year-old alcoholic patient with cirrhosis who died in a coma hepatic encephalopathy which shows both normal astrocytes (N), which have dark nuclei, and Alzheimer type II astrocytes, characteristic of hepatic encephalopathy, having pale, enlarged nuclei

4. EPIDEMIOLOGY AND PROGNOSIS

The risk of developing hepatic encephalopathy is 20% per year, and at any time about 30–45% of people with cirrhosis exhibit evidence of overt 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. [21]

5. CONCLUSION

Hepatic encephalopathy is a major neuropsychiatric complication of alcoholic liver disease and an important contributor to the cognitive dysfunction found in chronic alcoholic patients. Hepatic encephalopathy is caused in part by the accumulation in the brain of neurotoxic substances such as ammonia and manganese, which normally are removed by the hepato-biliary system. Increased brain concentrations of ammonia alter the expression of genes that encode important brain proteins responsible for regulating neurotransmitters; higher levels of ammonia also alter the structure of brain cells called astrocytes. Manganese deposited in basal ganglia structures (particularly the globuspallidus) in patients with alcoholic cirrhosis leads to impaired motor function and the appearance of distinct, abnormally intense signals, which can be detected by MRI. Prevention and

treatment of hepatic encephalopathy in alcoholic cirrhotic patients continue to rely on strategies aimed at lowering blood ammonia concentrations. Current research is focused on identifying neurological and biochemical mechanisms underlying hepatic encephalopathy as well as pharmacotherapies that can address these mechanisms, and on creating liver-assist devices aimed at removing toxins from the blood. Liver transplantation is used in chronic alcoholic patients with end-stage liver failure.

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