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Review Article

HEPATIC ENCEPHALOPATHY - A COMPLICATION OF LIVER DISEASE

M. C. Dhorajiya., V. J. Galani*

Department of Pharmacology, A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar-388120. India.

ABSTRACT

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome characterized by severe cognitive, psychiatric, and motor disturbances resulting from acute or chronic liver failure. Elevated plasma and central nervous system ammonia levels are considered key factors in its pathogenesis. Altered functions of astrocytes may also play an important role in the pathogenesis of HE. Brain ammonia is metabolized in astrocytes to glutamine, and increased glutamine accumulation in these cells may contribute to cytotoxic brain edema. Hepatic encephalopathy complicating chronic liver failure appears to be associated with a shift in the balance between inhibitory and excitatory neurotransmission towards a net increase of inhibitory neurotransmission. Changes in serotonergic, dopaminergic, cholinergic and endocannabinoids seem to involved in the pathogenesis of HE. Oxindole, a tryptophan metabolite has been shown to accumulate in cirrhotic patients and animal models of HE. Empiric therapy for HE is largely based on the principle of reducing the production and absorption of ammonia in the gut and increase ammonia clearance from the central nervous system through administration of pharmacological agents such as nonabsorbable disaccharides, zinc, antibiotics, ornithine aspartate, sodium benzoate etc.

Key words: Hepatic encephalopathy, ammonia, astrocytes, liver disease

INTRODUCTION

Hepatic encephalopathy (HE) and portal–systemic encephalopathy are the terms used interchangeably to describe a complex neuropsychiatric syndrome associated with acute or chronic hepatocellular failure, increased portal systemic shunting of blood, or both. Hepatic encephalopathy complicating acute liver failure is referred to as fulminant hepatic failure. The neurological impairment in HE is a continuous spectrum which can be broadly divided into two categories, overt hepatic encephalopathy and covert hepatic encephalopathy.[1] Overt hepatic encephalopathy is associated with a syndrome of neurological and neuropsychiatric abnormalities such as asterixis, hyper-reflexia and with slow dominant rhythm on electroencephalography that can be detected by bedside clinical tests and is easy to diagnose. Covert HE is a new term introduced at the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (2011) to

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encompass minimal hepatic encephalopathy present with normal mental and neurological status upon clinical examination but specific psychometric tests yield abnormal results.[1,2] A classification system for HE disorders was devised by the working party at the 1998 world Congress of Gastroenterology in vienna, austria (Table 1).[3]
Patients with HE suffer from sleep disturbances, changes of mood and personality, severe cognitive effects (e.g., a shortened attention span), psychiatric conditions such as anxiety and depression, as well as motor disturbances, including motor incoordination and a type of flapping tremor of the hands called asterixis. In the most serious cases, the patients no longer respond to external stimuli and may fall into a coma (i.e., hepatic coma), which can be fatal.[4]

The present review focus on the biochemical alterations/ammonia associated with HE that contributes to the clinical manifestations of HE and treatment approaches of HE.

Table 1. Classification of hepatic encephalopathy by working party.

Type	Nomenclature		
A	Hepatic Encephalopathy associated with acute liver failure		
B	Hepatic Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease		
C	Hepatic Encephalopathy associated with cirrhosis and portal hypertension or portal-systemic shunts	Subcategory	Subdivisions
		Episodic HE	Precipitated Spontaneous (without identifiable precipitating factor) Recurrent
		Persistent HE	Mild Severe Treatment dependent
		Minimal HE	

HE: Hepatic encephalopathy

ETIOLOGY OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is caused by disorders that affect the liver. These include disorders that reduce liver function (such as cirrhosis or hepatitis) and conditions in which blood circulation does not enter the liver. An important function of the liver is to change toxic substances that are either made by the body or taken into the body (such as medicines) and make them harmless. However, when the liver is damaged, these "poisons" may build up in the bloodstream. Ammonia, which is produced by the body when proteins are digested, is one of the harmful substances that are normally made harmless by the liver. Many other substances may also build up in the body if the liver is not working well. They can cause damage to the nervous system.Hepatic encephalopathy may occur suddenly in people who previously had no liver problems when damage occurs to the liver. More often, the

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condition is seen in people with chronic liver disease. Hepatic encephalopathy may be triggered by dehydration, excess protein intake, electrolyte abnormalities (especially a decrease in potassium), bleeding from the intestines, stomach, or esophagus, infections (Pneumonia, urinary tract infection, spontaneous bacterial peritonitis, other infections), kidney problems, low oxygen levels in the body, shunt placement or complications (Transjugular intrahepatic portosystemic shunt), surgery, and use of medications that suppress the central nervous system (sedatives such as benzodiazepines, narcotics and sedative antipsychotics). Disorders that can mimic or mask symptoms of hepatic encephalopathy include Alcohol intoxication, complicated alcohol withdrawal, meningitis, metabolic abnormalities such as low blood glucose, sedative overdose, subdural hematoma (bleeding under the skull), and Wernicke-Korsakoff syndrome. [5,6] Hepatic encephalopathy may occur as an acute, potentially reversible disorder. It may occur as a chronic, progressive disorder that is associated with chronic liver disease.

PATHOPHYSIOLOGY OF HEPATIC ENCEPHALOPATHY

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte function. Astrocytes account for about one third of cortical volume. They play a key role in the regulation of the blood-brain barrier. They are involved in maintaining electrolyte homeostasis and in providing nutrients and neurotransmitter precursors to neurons. They also play a role in the detoxification of a number of chemicals, including ammonia.[7]

Role of ammonia

Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines, and urea. Enterocytes also convert glutamine to glutamate and ammonia by the activity of glutaminase.[8] Normally, ammonia is detoxified in the liver by conversion to urea by the Krebs-Henseleit cycle. A defect in one of the six urea cycle enzymes and two membrane transporters results in so called primary hyperammonemia, while metabolic defects outside the urea cycle as well as side effects of drugs can lead to secondary hyperammonemia. Inborn errors of metabolism result in accumulation of toxic products which can lead to inhibition of other metabolic pathways. This is also the case for the urea cycle which can lose its ammonia detoxifying capacity because accumulating metabolites can impair the synthesis of N-acetylglutamate, the obligate activator of carbamyl phosphate synthase-1. Increased ammonia production caused by bacterial overgrowth can occur in bladders, uretero-sigmoid shunts or within the intestine.[9] Ammonia is also consumed in the conversion of glutamate to glutamine, a reaction that depends upon the activity of glutamine synthetase. Two factors contribute to the hyperammonemia that is seen in cirrhosis. First, there is a decreased mass of functioning hepatocytes, resulting in fewer opportunities for ammonia to be detoxified by the above processes. Secondly, portosystemic shunting may divert ammonia containing blood away from the liver to the systemic circulation.

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Normal skeletal muscle cells do not possess the enzymatic machinery of the urea cycle but do contain glutamine synthetase. Glutamine synthetase activity in muscle actually increases in the setting of cirrhosis and portosystemic shunting. Thus, skeletal muscle is an important site for ammonia metabolism in cirrhosis. However, the muscle wasting that is observed in patients with advanced cirrhosis may potentiate hyperammonemia. The kidneys express glutaminase and, to some extent, play a role in ammonia production. However, the kidneys also express glutamine synthetase and play a key role in ammonia metabolism and excretion.[8] Brain astrocytes also possess glutamine synthetase. However, the brain is not able to increase glutamine synthetase activity in the setting of hyperammonemia. Thus, the brain remains vulnerable to the effects of hyperammonemia. Ammonia has multiple neurotoxic effects. It can impair amino acid metabolism and energy utilization in the brain. Ammonia can also inhibit the generation of excitatory and inhibitory postsynaptic potentials. It can alter the transit of amino acids, water, and electrolytes across astrocytes and neurons. As glutamine is an osmolyte, water moves inside the astrocyte causing it to swell. This swelling leads to cerebral edema and intra-cranial hypertension.[10] Administration of methionine sulfoximine (an inhibitor of glutamine synthase) prevents astrocyte swelling in experimental animals.[11]

In astrocytes, prolonged exposure to increased concentrations of ammonia induces a number of changes. Astrocyte swelling is, in part, compensated for by release of the osmolytes myoinositol and taurine from the cell.[12] This homeostatic mechanism results in depletion of intracellular myoinositol stores; low intracellular myoinositol levels are associated with an increased risk of sudden deterioration of HE.[13] Activity of glutamate receptors in the postsynaptic plate are downregulated and glutamate transporters on the astrocyte cell membrane are inactivated.[14] Over time, some of these cells change in shape and form and become 'Alzheimer type II' astrocytes, as observed in both *in vitro* studies and in human autopsy specimens.[15,16]

Role of manganese

Manganese is a neurotoxin that preferentially accumulates in the basal ganglia. Manganese deposition has been detected by MRI in the basal ganglia of patients with cirrhosis and in rats with an extensive portacaval shunt[17,18]–and has been shown to resolve with normalization of liver function.[19,20] Manganese is thought to induce changes in astrocytes of the basal ganglia that promote the formation of Alzheimer type II astrocytes. This neurotoxin is also involved in stimulation of translocator proteins on astrocytes, which further enhances neurosteroid synthesis and GABAergic tone.[21] Preferential deposition of manganese in the basal ganglia might explain the Parkinsonian symptoms (such as tremors) seen in some patients with HE.[22]

Changes in cerebral energy metabolism

Patients with HE have decreased cerebral blood flow and decreased consumption of glucose and oxygen.[23] Positron emission tomography scanning has shown correlations between

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alterations in cerebral blood flow and the severity of neuropsychological function.[24] In animal models, abnormalities in cerebral energy metabolism occur after the onset of coma.[25] Extrapolation of this model to human beings is difficult, but changes in cerebral blood flow and glucose metabolism may be an epiphenomenon, secondary to a global depression in the function of the central nervous system, rather than the cause of HE.

Changes in cerebral neurotransmission

The normal state of wakefulness is determined by a fine balance between the state of excitatory and inhibitory neurotransmission.

Glutamatergic neurotransmission

Glutamate is the major excitatory neurotransmitter in the mammalian brain in that it acts at about 80% of all brain synapses. Neuronal inhibition in uncomplicated liver failure is associated with decreased glutamatergic tone. Ammonia-induced depolarization of nerve cells in vivo or in vitro has been shown to increase the calcium-dependent release of glutamate in various brain regions. An obvious direct consequence of this excessive glutamate release is overstimulation of the ionotropic glutamate receptors, in particular the NMDA receptors. The critical role of activated NMDA receptors in fulminant hepatic failure has been convincingly demonstrated in a study by Vogels et al.[26] Ammonia-induced activation of NMDA receptors elicits metabolic events that may lead to irreversible neuronal dysfunction and damage. These events include (a) an increase of the Na^+, K^+-ATPase activity in nerve cell membranes[27-29], (b) proteolysis of the microtubule-associated protein 2 (MAP-2)[30] and (c) increased generation of nitric oxide.[28]

Prolonged exposure to increased concentrations of ammonia in HE down-regulates NMDA receptors. The decreased Glutamate receptor density likely contributes to decreased excitatory transmission in HE. Hermenegildo et al.[31] have shown by *in vivo* brain microdialysis that chronic, mild hyperammonemia in rats inhibits NMDA induced liberation of cGMP into the extracellular space. This finding was interpreted as reflecting an ammonia evoked impairment of the glutamate–NO–cGMP pathway. Since, this pathway is involved in long-term potentiation (LTP), a phenomenon underlying memory formation, its inhibition may contribute to HE related deficits in intellectual and memory function of humans.

Glutamine synthesis from ammonia and glutamate occurs in a reaction catalyzed by glutamine synthetase, which is an astrocyte-specific enzyme. Accordingly, increased accumulation of glutamine in the brain is the rule in several hyperammonemic conditions. Evidence implicates glutamine accumulation as a major cause of astrocytic swelling and, subsequently, an increase in the water content of the whole brain and it is responsible for cerebral edema. Cerebral edema is a major cause of intracranial hypertension and death in patients with HE.

GABAergic system

Ammonia may indirectly increase GABA-ergic neurotransmission and also inhibit the function of CNS by synergistic activity with natural benzodiazepine receptor ligands.[32] Presynaptic $GABA_B$ activation inhibits

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depolarization induced GABA release. Loss of $GABA_B$ receptors was observed with Thioacetamide (TAA) which probably raise brain GABA release.[33] It is also responsible for sedative and depressant effects in rats.

Serotonergic system

Basal serotonin levels were found to be unchanged in cerebral cortical microdialysates of rats with portacaval shunts,[34] and of rats with thioacetamide-induced HE. [35] However, a significant increase of extracellular serotonin was induced by ammonia challenge in a rat model of HE compared to control rats.[34] Thus, increased serotoninergic inhibitory tone may contribute to some manifestations of HE. Serotonergic mechanisms contribute to behavioral manifestation of hepatic encephalopathy induced by TAA. Increased in serotonergic inhibitory tone may contribute to fall down of locomotor activity in TAA treated rats. Improvement of locomotor activity was reported with wide spectrum serotonin antagonist methysergide.[36] TAA induced hepatic encephalopathy in rats is associated with down regulation of 5-HT_{2A} receptors.[35]

Dopaminergic system

Changes in whole brain content of dopamine and its metabolites have frequently been reported in animal models of HE, and in cirrhotic patients who died with HE.[37] A loss of striatal dopamine D_2 receptors[38] and increased activities of the dopamine metabolizing enzymes MAO-A and MAO-B, have been reported in brain tissue of cirrhotic patients of HE.[39] These finding reported that a decrease in dopaminergic tone may contribute to motor disturbances in HE.

Cholinergic system

Acetylcholinesterase (AChE) is a membrane-bound enzyme involved in cholinergic neurotransmission, which hydrolyzes acetylcholine released from presynaptic terminals obstructing acetylcholine transmission.[40] Recently, it has been demonstrated that AChE was severely decreased in the brain cortex of an experimental model of acute liver failure by TAA[41] whereas in bile duct ligated rats, it was increased and no changes were observed in the portal-systemic HE.[42] Cholinergic neurotransmission is one of the most important means of neurotransmission in the mammalian brain. Cortical acetylcholine mediates sustained and selective attention, arousal, alertness, wakefulness and electroencephalographic desynchronization.[43] The activity of AChE is altered in neuropsychological disorders such as Alzheimer's disease and dementia,[44] which show disturbance of learning and memory processes. Considering that impaired spatial learning and active avoidance behaviour have been described in rats with chronic liver failure by TAA administration.[45]

Endocannabinoids

Endocannabinoids function as neurotransmitters and neuromodulators in the central nervous system via specific receptors and apparently have a neuroprotective role. The endocannabinoid system could be involved in the pathogenesis of hepatic encephalopathy (HE), a neuropsychiatric syndrome due to liver disease. Researcher used a mouse model of a thioacetamide induced hepatic encephalopathy.[46] They found that the levels of the endocannabinoid 2-arachidonoyl-glycerol (2-AG) were

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elevated in the brain. Treatment with either 2-AG or with the CB1 receptor antagonist, SR141716A, improved a neurological score, activity and cognitive function. Activation of the CB2 receptor by a selective agonist, HU308, also improved the neurological score. 2-AG activity could be blocked with the specific CB2 receptor antagonist SR144528A. The CB1 receptor agonist noladin ether was inactive. It concluded that the endocannabinoid system may play an important role in the pathogenesis of HE. Modulation of this system either by exogenous agonists specific for the CB2 receptors or possibly also by antagonists to the CB1 receptors may have therapeutic potential.[46]

Oxindole

Oxindole is a tryptophan metabolite in the two-step indole pathway. Its synthesis in animal tissues is promoted by gut bacteria. When administered intraperitoneally, it produces strong sedative and hypotensive effects in the rat.[47] Oxindole was found to accumulate in the blood of cirrhotic patients to a greater extent if HE was present, and in the blood and brain of rats with thioacetamide or galactosamine induced HE.

In general terms, the new data are consistent with the progression of HE to coma being associated with increasing efficiency of the inhibitory neurotransmitter systems (GABA-benzodiazepine, serotonin) and depression of the function of the excitatory glutamatergic system. Some of the impairment of motor function in HE is probably due to decreased dopaminergic tone related to the glutamatergic dysfunction.

CLINICAL FEATURES AND DIAGNOSIS

Patients with HE can present with a variety of clinical features ranging from life-threatening coma with cerebral edema (most often in fulminant hepatic failure) to subclinical, occult or minimal. Many symptoms like, confusion/disorientation, breath with a musty or sweet odour, change in sleep patterns and thinking, confusion that is mild, forgetfulness, mental fogginess, personality or mood changes, poor concentration and judgment, worsening of handwriting or loss of other small hand movements.

More severe clinical features may include abnormal movements or shaking of hands or arms, agitation, excitement, or seizures (occur rarely), disorientation, drowsiness or confusion, inappropriate behaviour or severe personality changes, slurred speech, slowed or sluggish movement.[48]

The clinical features of encephalopathy in fulminant liver failure are essentially the same as those seen in patients with cirrhosis but as cerebral edema is more common in these patients, signs of raised intracranial pressure (bradycardia, hypertension, dilated pupils, decerebrate posturing) may also be seen.[49] The severity of hepatic encephalopathy is graded with the West Haven Criteria;[3] this is based on the level of impairment of autonomy, changes in consciousness, intellectual function, behaviour, and the dependence on therapy. (Table 2).

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Table 2. Grading mental state in hepatic encephalopathy according to West Haven criteria

Grade	Mental state
0	No abnormality detected
1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
2	Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour
3	Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

Intrinsically linked to the diagnosis of HE is an evaluation of the degree of liver dysfunction and possible alterations of the hepatic circulation (thrombosis, large spontaneous portal-systemic shunt, transjugular intrahepatic portal-systemic shunt [TIPS]). The detection of asterisks, fetor hepaticas, and fluctuating long-tract signs are helpful clues, albeit nonspecific. The absence of such clinical signs does not exclude the diagnosis of HE.

Measurement of venous ammonia blood levels may be helpful in the initial evaluation when there is doubt about the presence of significant liver disease or of other causes for an abnormality in consciousness. Follow-up with repeated ammonia levels is unnecessary and does not replace the evaluation of the patient's mental state. A relation between ammonia levels and the risk of cerebral edema in cirrhosis[50] has not been examined. Ammonia levels should be promptly assayed in an experienced laboratory to avoid pitfalls in its determination.[51]

Tools to exclude other causes of an abnormal mental state include automated electroencephalogram analysis,[52] brain imaging (especially in patients in stupor and coma), and lumbar puncture (for patients with unexplained fever, leukocytosis, or other symptoms suggestive of meningeal irritation). Alterations of the electroencephalogram are not specific for HE and are subject to variability in interpretation; automated analysis of the tracings simplifies the diagnosis.[53] Neuropsychological testing can range from an extensive battery to a single test office-based screening approach. The number connection test, the digit symbol test and the block design test are most frequently employed.[54]

TREATMENT APPROACHES

Treatment of precipitating factors

It is necessary to identify precipitating events and implement immediate therapy as prompt action may lead to a permanent improvement in HE.[55] Though acute or chronic liver failure may be triggered by such uncommon events, such as sedatives or tranquillisers, vascular occlusion

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(hepatic vein or portal vein thrombosis) and hepatocellular carcinoma transformation, it is important to outline the management of the more common precipitants that are constipation, electrolyte and acid-base imbalance, infection, gastrointestinal bleeding, portal-systemic shunts.

Treatments to decrease intestinal ammonia production

1. Vegetable-based Protein

Vegetable-based protein is better tolerated by patients with cirrhosis than meat-based protein. Vegetable-based protein foods have a high fibre content, which increases intestinal transit time and colonic motility and enhances intestinal nitrogen clearance. Vegetable protein also reduces colonic pH, which prevents ammonia from being absorbed in the gut. The adverse effects of a predominantly vegetarian diet include abdominal bloating and flatulence. To reduce these effects and increase a patient's protein intake vegetable protein can be combined with dairy products, such as milk and cheese.[55]

2. Nonabsorbable Disaccharides

Nonabsorbable disaccharides include lactulose and lactitol (an analog of lactulose that is not available in USA). They are degraded by intestinal bacteria to lactic acid and other organic acids. Lactulose is considered the first-line therapy for HE. Lactulose appears to inhibit intestinal ammonia production by a number of mechanisms. The conversion of Lactulose to lactic acid results in acidification of the gut lumen. This favors conversion of NH_4^+ to NH_3 and the passage of NH_3 from tissues into the lumen. Gut acidification inhibits ammoniagenic coliform bacteria, leading to increased levels of non-ammoniagenic lactobacilli. Lactulose also works as a cathartic, reducing colonic bacterial load.

In addition to having a laxative effect, lactulose and lactitol reduce the colonic pH and interfere with mucosal uptake of glutamine in the gut, thereby reducing the synthesis and absorption of ammonia.[56] Initial lactulose dosing is 30 mL orally, daily or twice daily. The dose may be increased as tolerated. Patients should be instructed to reduce lactulose dosing in the event of diarrhea, abdominal cramping, or bloating. Patients should take sufficient lactulose as to have 2-4 loose stools per day.[57] Great care must be taken when prescribing lactulose. Overdosage can result in ileus, severe diarrhea, electrolyte disturbances, and hypovolemia. Hypovolemia may be sufficiently severe as to actually induce a flare of encephalopathy symptoms.[57]

3. Antibiotics

Neomycin and other antibiotics, such as metronidazole, oral vancomycin, paromomycin, and oral quinolones, are administered in an effort to decrease the colonic concentration of ammoniagenic bacteria. Initial neomycin dosing is 250 mg orally 2-4 times a day. Doses as high as 4000 mg/d may be administered. Neomycin was one of the first antibiotics to be investigated as a potential treatment for HE. This drug mainly works by inhibiting mucosal glutaminase in the intestine, which reduces ammonia production in the gut.[58] Neomycin inhibits ammoniagenic coliform bacteria that produce urease (an enzyme that converts urea into ammonia) and are prevalent in the gut. The main adverse effects of neomycin sulfate

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administration include ototoxic and nephrotoxic effects and intestinal malabsorption. Rifaximin a nonabsorbable derivative of rifampin has also been used in the treatment of hepatic encephalopathy.

Multiple clinical trials have demonstrated that rifaximin at a dose of 400 mg taken orally 3 times a day was as effective as lactulose or lactilol at improving hepatic encephalopathy symptoms.[59] Similarly, rifaximin was as effective as neomycin and paromomycin. Rifaximin was better tolerated than both the cathartics and the other nonabsorbable antibiotics.

Treatments to increase ammonia clearance

1. L-ornithine L-aspartate (LOLA)

LOLA is available in Europe in both intravenous formulations and oral formulations. It is not available in the United States. LOLA is a stable salt of the two constituent amino acids. L-ornithine stimulates the urea cycle, with resulting loss of ammonia. Both l-ornithine and l-aspartate are substrates for glutamate transaminase. Their administration results increased glutamate levels. Ammonia is subsequently used in the conversion of glutamate to glutamine by glutamine synthetase.[60] LOLA was found to be effective in treating hepatic encephalopathy in a number of European trials.

2. Zinc

Zinc deficiency is common in cirrhosis. Even in patients who are not zinc deficient, zinc administration has the potential to improve hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle.[61] The subsequent increase in ureagenesis results in the loss of ammonia ions. Zinc sulfate and zinc acetate have been used at a dose of 600 mg orally every day in clinical trials.

3. Sodium benzoate, sodium phenylbutyrate, sodium phenylacetate

Sodium benzoate interacts with glycine to form hippurate. The subsequent renal excretion of hippurate results in the loss of ammonia ions. Dosing of sodium benzoate at 5 g orally twice a day can effectively control hepatic encephalopathy.[62] Use of the medication is limited by the risk of salt overload and by its unpleasant taste. Sodium phenylbutyrate is converted to phenylacetate. Phenylacetate, in turn, reacts with glutamine to form phenylacetylglutamine. This chemical is subsequently excreted in the urine, with loss of ammonia ions. Sodium phenylbutyrate and intravenous sodium phenylacetate in combination with sodium benzoate (Ammonul) are approved by the FDA for the treatment of hyperammonemia associated with urea cycle disorders.[63] Ammonul is currently undergoing clinical trials in patients with cirrhosis, hyperammonemia, and severe hepatic encephalopathy.

4. L-carnitine

L-carnitine improved hepatic encephalopathy symptoms in several small studies of patients with cirrhosis.[64] Whether the medication works by improving blood ammonia levels or whether it works centrally perhaps by decreasing brain ammonia uptake remains unclear.

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5. Carglumic Acid

N-acetylglutamate synthatase (NAGS) deficiency is one of the urea cycle disorders (UCD). UCD are inherited metabolic disorders resulting from a deficiency in one of the six enzymes involved in urea synthesis, which leads to hyperammonaemia. Accumulation of ammonia in the body causes irreversible brain damage, coma, and eventually death. Carglumic acid is a structural analogue of N-acetylglutamate, which is the naturally occurring activator of carbamoyl phosphate synthetase, the first enzyme of the urea cycle. Carglumic acid is used for the treatment of acute hyperammonemia in patients with specific organic acidurias that can lead to NAG deficiency secondary to inhibition of NAGS. [65]

Counteract abnormalities of central neurotransmission

1. Flumazenil

Flumazenil causes short-term improvement of hepatic encephalopathy in patients with cirrhosis and acute or chronic hepatic encephalopathy. Flumazenil is a competitive benzodiazepine receptor antagonist. This drug has a high affinity for these receptors and can rapidly reverse the hypnotic effect of benzodiazepines.[66] In hepatic encephalopathy, the inhibitory effect of GABA-benzodiazepine on the central nervous system is antagonized by flumazenil. Flumazenil stops the binding of GABA to its receptors by benzodiazepine agonists. In cirrhotic patients, uncontrolled studies have shown a beneficial effect of flumazenil in hepatic encephalopathy. Several prospective randomized controlled trials have tested the clinical and electroencephalographic efficacy of flumazenil in HE.[67]

2. Dopaminergic agents (e.g., bromocriptine)

A loss of striatal dopamine D_2 receptors[39] and increased activities of the dopamine-metabolizing enzymes monoamine oxidase (MAO-A and MAO-B), have been seen in brain tissue of cirrhotic patients HE[38] These findings suggest that a decrease in dopaminergic tone may contribute to motor disturbances in HE. Modulation of motor behavior by striatal dopamine is influenced by glutamate acting on presynaptic NMDA receptors of dopaminergic neurons.

Bromocriptine may be indicated for patients with chronic encephalopathy unresponsive to other therapy. New studies have shown the presence of extrapyramidal symptoms in patients with cirrhosis and correlation between the symptoms and alterations in the basal ganglia, detected by magnetic resonance imaging and proton spectroscopy similar to Parkinson's disease.[68]

Removal of substances from the blood

Liver support systems

The incongruity that exists between donor organs and recipients has led to a plethora of extracorporeal liver assist devices (ELADs) to aid or supplant the failing liver.[41] ELADs are either:

- Biological (including hybrid & combination) devices: which use either immortalised hepatocytes cultured in bio-reactors or whole animal livers to mimic endogenous excretory and synthetic liver function.

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- Non-biological devices: which use extracorporeal blood purification to dialyse albumin- bound hydrophobic substances (e.g. ammonia, bilirubin, bile acids, aromatic amino acid metabolites and medium-chain fatty acids).

The extracorporeal devices under clinical evaluation include the following:

- Molecular adsorbent recirculating system (MARS): provides counter-current haemodialysis against albumin and bicarbonate circuits.
- Single-pass albumin dialysis (SPAD): provides counter-current albumin dialysis against high flow blood in a fibre haemodiafilter, which unlike MARS is discarded after passing the filter. As a standard renal dialysis device is used, continuous veno-venous haemodiafiltration is possible.
- Prometheus system: provides direct albumin adsorption with high-flux haemodialysis after selective filtration of the albumin fraction through a specific polysulfon filter.

All these devices successfully remove protein-bound toxins, but may have more variable effects on systemic (versus portal) haemodynamics; and worsen coagulopathy. Currently the clinical benefit of such devices is unclear, although they may offer a bridge to transplantation or liver recovery.

Liver transplantation

Although OLT (Orthotopic liver transplantation) dramatically improves the clinical status with a return to a normal mental state, there is evidence to suggest that minimal HE may persist in certain patients due to some as yet unknown irreversible changes in the brain.[69]

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