Compendium

Hepatic Encephalopathy: Etiology, Pathogenesis, and Clinical Signs

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Abstract: *Hepatic encephalopathy (HE) is a manifestation of clinical signs that may result from a variety of liver diseases. In small animals, HE is most commonly a result of portosystemic shunting. The pathogenesis is not completely understood, although it is likely multifactorial. Theories of pathogenesis include altered ammonia metabolism and glutamine and glutamate transmission, an increase in γ-aminobutyric acid agonists and benzodiazepine-like substances, alterations of the serotonergic system and amino acid metabolism, elevated taurine levels, contributions from inflammatory mediators, and toxic effects of manganese. An understanding of the underlying mechanisms that result in HE may lead to new treatments in the future.*

For more information, please see the companion article, "Hepatic Encephalopathy: Diagnosis and Treatment."

Hepatic encephalopathy (HE) is defined as an abnormal mental state with augmented neuronal inhibition in the central nervous system (CNS) resulting from liver dysfunction. It is caused by the accumulation of toxic byproducts that have not been adequately metabolized by the liver.[1,2] The causes of HE can be further classified by the type of liver disease present and the nature of the associated clinical signs.

Clinical Signs

The clinical signs of HE are usually divided into four stages.[1,3–5] Stage I occurs when gut-derived toxins are beginning to affect the CNS. Typical clinical signs include mild confusion, inappetence, dull demeanor, and mild irritability. The owner may be the only one to notice these subtle, nonspecific signs, and the patient may appear normal to the veterinarian. Stage II is characterized by lethargy, ataxia, markedly dull behavior, occasional aggressive behavior, head pressing, blindness, and salivation. The patient may seem disoriented. A patient with stage III HE is uncoordinated, confused in its surroundings, stuporous, and completely inactive but can be aroused. Severe ptyalism can be present, particularly in cats, and seizures may occur.[1,3,6,7] Cats with a portosystemic shunt (PSS) are more likely to have a seizure than dogs. Seizures alone, in the absence of other clinical signs of HE, are never due to HE.[3,7] Cats may also present with golden or copper-colored irises secondary to decreased hepatic metabolism.[6,7] Stage IV HE is characterized by recumbency, unarousable somnolence, and coma leading to death[1,3,4] (**TABLE 1**). It is characteristic for patients to fluctuate between stages I through IV in an episodic manner.[3]

In all stages of the clinical syndrome, animals may show non-neurologic signs related to the underlying disease, such as vomiting, diarrhea, and weight loss. Animals with portal hypertension and

Table 1. Stages of Hepatic Encephalopathy

Stage I	Stage II	Stage III	Stage IV
• Mild confusion	• Lethargy	• Incoordination	• Recumbency
• Inappetence	• Ataxia	• Confusion	• Complete unresponsiveness
• Dull demeanor	• Markedly dull behavior	• Stuporous	• Coma
• Mild irritability	• Personality changes	• Inactive but arousable	• Death
	• Head pressing	• Severe ptyalism	
	• Blindness	• Seizures	
	• Disorientation	• Occasional aggression	

Table 2. Congenital Portosystemic Shunts[6,11–13,a–c]

Intrahepatic Shunt	Extrahepatic Shunt
Ductus venosus remains patent	Abnormal communications between the fetal cardinal or vitelline venosus systems
Occurs in large-breed dogs (e.g., Irish wolfhounds, Labrador retrievers)	Most common type Occurs in cats and small- or toy-breed dogs (e.g., Yorkshire terriers, miniature schnauzers, Maltese, Havanese, pugs)
Onset of clinical signs usually <1 year of age	Onset of clinical signs usually >1 year of age

[a]GB. Effect of breed on anatomy of portosystemic shunts resulting from congenital diseases in dogs and cats: a review of 242 cases. *Aust Vet J* 2004;82(12):746-749.

[b]Johnson CA, Armstrong PJ, Hauptman JG. Congenital portosystemic shunts in dogs: 46 cases (1979-1986). *J Am Vet Med Assoc* 1987;191(11):1478-1483.

[c]Tobias KM, Rohrbach BW. Association of breed with the diagnosis of congenital portosystemic shunts in dogs: 2400 cases (1980-2002). *J Am Vet Med Assoc* 2003;223(11):1636-1639.

Box 1. Causes of Acute Liver Disease[3,16,a]

Toxins
- Acetaminophen
- Potentiated sulfonamides
- Aflatoxins
- Amanita mushrooms
- Xylitol
- Cycad seeds
- Blue-green algae

Infectious
- Canine hepatitis
- Feline infectious peritonitis
- *Toxoplasma* spp
- *Neospora* spp
- Leptospirosis
- *Histoplasma* spp
- Caval syndrome due to dirofilariasis

Ischemic insults
- Severe hypotension
- Hemolytic anemia
- Arterial or venous occlusion
- Neoplasia
- Lymphoma
- Malignant histiocytosis

Metabolic disease
- Hepatic lipidosis in cats (due to arginine depletion)
- Copper storage disease (Bedlington terriers, West Highland white terriers, Dalmatians)

[a]Morris JG, Rogers QR. Ammonia intoxication in the near-adult cat as a result of a dietary deficiency of arginine. *Science* 1978;199(27):431-432.

moderate to severe hypoalbuminemia (<2.0 g/dL) secondary to liver dysfunction may develop ascites.[3] Polyuria and polydipsia are common manifestations of HE in dogs with a PSS as a result of hypercortisolism and inhibition of arginine vasopressin release.[8–10] Insufficient growth and dysuria due to ammonium biurate crystals may be seen if a congenital PSS or chronic hyperammonemia is present.[3,6,11] PSSs are vascular abnormalities that permit the portal blood to bypass the liver and enter systemic circulation directly.[11] Most cases of HE in cats and dogs are due to a single congenital PSS[7,11–13] (**TABLE 2**).

The onset of clinical signs is usually within the first year of life if a congenital PSS is present.[11] Although congenital PSSs are typically identified in dogs younger than 2 years, they cannot be ruled out in older animals presenting with encephalopathic signs.[14] Unlike dogs with a macroscopic congenital PSS, most dogs with portal vein hypoplasia do not develop clinical signs of HE.[15] Animals with acquired hepatic disorders typically develop clinical signs as adults (older than 1 year).[11] In acute HE (**BOX 1**), clinical signs are indicative of elevated intracranial pressure and include hypertension, bradycardia, irregular respirations, decerebrate posture, and pupillary abnormalities. They progress rapidly in a sequence of agitation, delirium, convulsions, and coma. Death may result from brain herniation.[16,17] Clinical signs of chronic HE typically present gradually and episodically and are usually precipitated by an underlying risk factor.[3,6]

Etiology

In human medicine, HE has been categorized into three types based on the nature of liver dysfunction present, and these categories have been adopted for veterinary use. Type A is associated with acute liver failure.[18,19] Type B is associated with portal-systemic bypass without intrinsic liver disease.[18,19] Type C is associated with severe hepatic parenchymal disease and portal hypertension

and is often complicated by the presence of multiple acquired PSSs.[18,19]

Type A encephalopathy occurs in cases of acute, severe liver disease (**BOX 1**) and manifests with a sudden onset of clinical signs, which can be rapidly progressive. Encephalopathy develops due to exposure of the brain to products released by the necrotic liver and can be complicated by systemic inflammatory response syndrome (SIRS) and hypoglycemia.[20,21] This type of HE frequently results in acute cerebral edema and intracranial hypertension, which are responsible for the neurologic abnormalities seen.[2,22] Histopathology of the brain in humans and animals with acute encephalopathy reveals astrocytic swelling,[23] contributing to cerebral edema. Type A HE is one of the factors that defines acute hepatic failure, and its presence is a poor prognostic indicator.[17]

Type B encephalopathy is the type most commonly seen in small animal patients with intrahepatic and extrahepatic PSSs.[6,11] Cairn terriers are predisposed to portal vein hypoplasia without portal hypertension (formerly known as *hepatic microvascular dysplasia*), a congenital disorder in which multiple shunting vessels within the liver bypass the hepatic sinusoidal system, rather than one grossly visible abnormal vessel.[11] In cats and dogs, rare congenital deficiencies of one of the enzymes involved in ammonia metabolism can result in severe hyperammonemia and HE in the absence of a PSS or intrinsic liver pathology.[24–36]

Type C encephalopathy is the most common type in humans.[19] In dogs and cats with long-standing liver disease, type C HE can

Box 2. Brain Neurotoxins and Neuroinhibitors Implicated in the Pathogenesis of Hepatic Encephalopathy	
• Ammonia	• Tryptophan/serotonin
• Glutamine	• Aromatic amino acids
• γ-Aminobutyric acid	• Manganese
• Benzodiazepine-like substances	• Opioids

occur with acquired PSSs from chronic portal hypertension.[11,27] Underlying liver disorders can be inflammatory, congenital, or vascular and include congenital arterioportal fistulas, hepatic cirrhosis, chronic hepatitis, and portal vein hypoplasia.[28] Acquired PSSs can develop in dogs of any breed or age.[28]

In animals, chronic HE associated with type B or C encephalopathy is characterized by episodic clinical signs that develop gradually. The patient may appear neurologically normal between episodes.[3] Histopathology of brain tissue from human and animal patients with chronic liver dysfunction reveals Alzheimer type II astrocytosis, which is characterized by swollen astrocytes, enlarged nuclei, and displacement of the chromatin to the perimeter of the cell.[1,11,23]

Pathogenesis

The pathogenesis of HE is complex and is likely a culmination of multiple factors. No single abnormality of hepatic or neurologic metabolism adequately explains all of the clinical, biochemical, and physiologic findings of HE, although hyperammonemia has been found to be play a key role in the development of HE[23] (**BOX 2**). The following theories on the pathogenesis of HE shape the current treatment recommendations.

Altered Ammonia Metabolism

Ammonia is generated in the body by four mechanisms: (1) degradation of intestinal protein and urea in the colon by urease-producing microorganisms, (2) intrahepatic metabolism of amino acids obtained from the diet, (3) enterocyte metabolism of glutamine, and (4) peripheral tissue (muscle) catabolism.[1,23,29] More than 50% of blood ammonia is derived from the intestinal breakdown of protein and urea.[23,29] During normal metabolism, ammonia reaches the liver from the portal circulation. Most of the ammonia then enters the urea cycle, resulting in the ultimate formation of urea, which is subsequently excreted by the kidneys (**FIGURE 1**).[29] The rest of the ammonia is used in the conversion of glutamate into glutamine by glutamine synthetase within various tissues within the body, such as the muscle, brain, and liver. The end product, glutamine, enters the circulation and is metabolized in the intestinal mucosa and kidneys to liberate the ammonia again.[3]

The ammonia hypothesis is central to the pathogenesis of acute and chronic HE. This hypothesis states that the major mechanism of HE is excessive accumulation of ammonia.[23] Liver dysfunction reduces the capabilities of ammonia detoxification, while portosystemic shunting detours ammonia-rich blood away from the liver into the systemic circulation, resulting in hyperammonemia.

The brain is devoid of a urea cycle. It relies instead on glutamine formation in astrocytes for effective removal of ammonia.[30] Nerve stimulation releases glutamate, an excitatory neurotransmitter, from presynaptic neurons. Astrocytes take up excess glutamate from the synaptic cleft. This glutamate, in conjunction with blood-derived ammonia, is metabolized to glutamine by glutamine synthetase. Glutamine is then actively extruded from astrocytic cells and taken up by presynaptic nerve terminals for conversion back to glutamate and subsequent utilization in neurotransmission.[23] Thus, astrocytes function to protect the brain from excessive neurotransmission.

In states of hyperammonemia, ammonia favors glutamine formation but impairs glutamine release from astrocytes. This results in accumulation of glutamine within astrocytic cells. The osmotically active glutamine causes cellular swelling, leading to neuronal edema[23] (**FIGURE 2**). Cellular edema is exacerbated by further ammonia metabolism within the astrocyte, a concept known as the "Trojan horse" hypothesis.[31] This hypothesis states that once ammonia interacts with glutamate in astrocytes to form glutamine, the glutamine enters the mitochondria. There, it is cleaved by glutaminase back to ammonia and glutamate. The resulting elevation in mitochondrial ammonia causes the production of reactive nitrogen and oxygen species[21,32] and failure of astrocytes to adequately regulate their intracellular volume.[31,33–37]
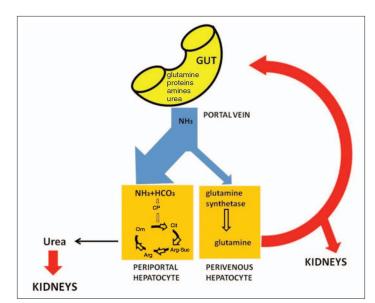

Figure 1. Ammonia metabolism. Ammonia (NH_3) is generated by degradation of proteins and urea in the gut and enterocyte metabolism of glutamine. Ammonia reaches the periportal hepatocyte via the portal vein, where the majority combines with bicarbonate to become carbamoyl phosphate (*CP*). CP enters the urea cycle, forming citrulline (*Cit*), then arginosuccinate (*Arg-Suc*), then arginine (*Arg*), and then ornithine (*Orn*). Urea produced by the urea cycle enters systemic circulation to be excreted by the kidneys. Ammonia not metabolized into urea is taken up by perivenous hepatocytes for conversion to glutamine, which undergoes either renal excretion or enterohepatic recirculation to be taken up by enterocytes. This prevents ammonia from entering the systemic circulation.[29]
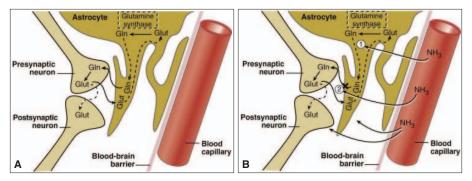
Figure 2. Glutamine and glutamate in the CNS. (**A**) Nerve stimulation releases glutamate (*Glut*) from the presynaptic neuron to serve as an excitatory neurotransmitter. To suppress neuronal excitation, astrocytes take up excessive glutamate from the synaptic cleft, where it is converted into glutamine (*Gln*) via glutamine synthase. Glutamine is then released into the presynaptic neuron, where it is converted back to glutamate for future neuroexcitation. (**B**) Ammonia freely diffuses across the blood-brain barrier and stimulates formation of glutamine by the astrocyte (1). Ammonia also blocks the export of glutamine from the astrocyte at the synaptic cleft (2). The result is increased astrocytic glutamine concentration, which promotes astrocyte swelling. *Reprinted with permission.*[21]

This leads to further cytotoxic cerebral edema[31] (**FIGURE 3**). Ammonia accumulation also results in reduction of cerebral glucose and oxygen metabolism,[34,38,39] redistribution of blood flow from the cerebral cortex to the subcortical regions of the brain,[34,38,40] and increased permeability of the blood-brain barrier to ammonia.[40]

Astrocyte swelling is a critical component of acute HE. When brain edema occurs in type A HE, it can lead to increased intracranial pressure, brain herniation, and death.[35] Low-grade cerebral edema is believed to occur in patients with types B and C HE.[41,42] Despite the many effects of hyperammonemia on the brain, blood ammonia levels do not correlate with the severity of clinical signs of HE,[3] which suggests that ammonia may not be the only player in the development of HE.

Inflammation

Infections and SIRS are common in patients with liver impairment. In humans, neurologic status deteriorates after induction of hyperammonemia in the inflammatory state, but not after resolution of the inflammation, suggesting that the inflammation and its mediators may be important in modulating the cerebral effect of ammonia in chronic and acute liver disease.[20,21,43,44] Lipopolysaccharide, a compound found on bacterial cell walls that is commonly implicated in sepsis and infections, enhances ammonia-induced changes in cerebral blood flow.[45,46] Additionally, neutrophils and inflammatory cytokines such as tumor necrosis factor a and interleukin 6 are known to induce cerebral swelling through production of reactive oxygen species.[43,44] Possible theories explaining how inflammation contributes to HE include cytokine-mediated changes in blood-brain barrier permeability, altered glutamate uptake by astrocytes, and altered expression of γ-aminobutyric acid (GABA) receptors.[43,44,47] Recent studies using ibuprofen have demonstrated improvement of mild encephalopathy in rats with chronic liver failure due to portocaval shunts,[48] and treatment with minocycline, a potent inhibitor of inflammatory cytokine production, attenuates the encephalopathy stage and prevents

brain edema in experimental acute liver failure.[49] Hence, antiinflammatory agents may be a target for future treatment of acute and chronic HE.[20]
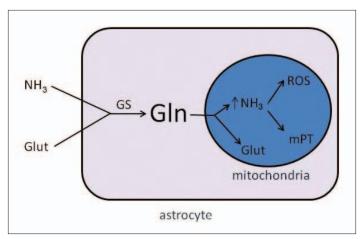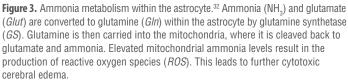
Alterations in Glutamate Transmission

The CNS glutamatergic neurotransmitter system is altered in animals with acute and chronic HE. As described above, astrocytes protect the brain from excessive neurotransmission by inactivating glutamate released from presynaptic nerve terminals. Hyperammonemia decreases glutamate uptake by astrocytes, which may result in elevated extracellular glutamate levels.[50] Downregulation of the glutamate transporter GLT-1, an essential transporter in the inactivation of glutamate at the synapse, has been shown in hyperammonemic rats, in rats with portocaval anastomosis, and in rats with experimentally induced liver failure.[51,52] High ammonia concentrations seen in stage IV HE inactivate neuronal chloride extrusion pumps, suppress inhibitory postsynaptic potential formation, depolarize neurons, and, therefore, promote increased neuronal excitation and a preconvulsive state.[53] Therefore, overstimulation by increased glutamate concentrations at synapses can result in seizures in animals with types A, B and, less commonly, C HE.[53,54]

Increase in γ-Aminobutyric Acid Agonists

The GABA hypothesis states that an excess of, or an increased sensitivity to, GABA (an inhibitory CNS neurotransmitter) is responsible for HE.[55] In a rabbit model of acute liver failure that progressed to coma, visual-evoked potentials measured were

Figure 3. Ammonia metabolism within the astrocyte.[32] Ammonia (NH_3) and glutamate (*Glut*) are converted to glutamine (*Gln*) within the astrocyte by glutamine synthetase (*GS*). Glutamine is then carried into the mitochondria, where it is cleaved back to glutamate and ammonia. Elevated mitochondrial ammonia levels result in the production of reactive oxygen species (*ROS*). This leads to further cytotoxic cerebral edema.
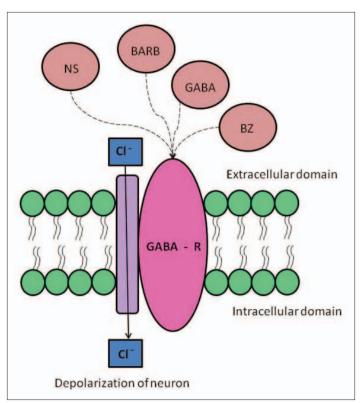
Figure 4. The GABA receptor complex. The GABA receptor complex is composed of the GABA receptor (*GABA-R*) and chloride channel. Binding of GABA to GABA-R opens the chloride channel, hyperpolarizing the neuronal membrane and inhibiting neurotransmission. Activation of the receptor complex by benzodiazepines (*BZ*), barbiturates (*BARB*), and neurosteroids (*NS*) potentiates the binding of GABA to GABA-R.

identical to those of a coma induced by drugs that activate the GABA receptor complex, such as benzodiazepines, barbiturates, and GABA agonists.[55] Further support for this hypothesis comes from human and animal studies showing the reversal of behavioral and electrophysiologic manifestations of HE by GABA receptor antagonists, such as flumazenil.[4,56–58]

GABA originates from the intestinal tract. Plasma levels of GABA increase with liver dysfunction due to decreased hepatic extraction. In acute liver failure or type A HE, the blood-brain barrier is more permeable[55]; as a result, increased GABA enters the brain and activates GABA receptor complexes, inducing the opening of chloride channels. As a result, the neuronal membrane becomes hyperpolarized and inhibits neurotransmission.[55] There is no evidence of increased blood-brain barrier permeability in dogs with a PSS or cirrhosis, and this mechanism does not appear to be a factor in the pathogenesis of types B and C HE.[59]

The GABA receptor complex binds many substances in addition to GABA, including benzodiazepines and barbiturates.[55] The binding of benzodiazepines to the benzodiazepine receptor induces a conformational change in the GABA receptor complex, enhancing its ability to bind GABA[55] (**FIGURE 4**). The increased GABAergic tone present in HE enhances the sedative and anesthetic effects of these drugs, which should be avoided in patients with HE.[3]

Increase in Benzodiazepine-like Substances

The GABA hypothesis predicts that benzodiazepines increase the severity of clinical signs of HE.[55] Laboratory rats, human patients, and dogs with acute and chronic HE have been found to have increased plasma levels of endogenous benzodiazepine-like substances due to decreased liver filtration.[60–62] Benzodiazepine-like substances originate from intestinal flora, vegetables in the diet, and psychiatric medication.[45,47,56,62,63]

Peripheral-type benzodiazepine receptors located on the outer mitochondrial membrane of astrocytes are increased in acute and chronic HE.[64–67] These receptors play a role in the synthesis of the neurosteroids tetrahydroprogesterone and tetrahydrodeoxycorticosterone, which are potent agonists of the GABA receptor.[53,54,68]

The GABA-ergic neurotransmission hypothesis and the ammonia hypothesis are not mutually exclusive. In studies using radioligand binding assays, ammonia was found to directly enhance inhibitory GABA neurotransmission and synergistically augment the potency of endogenous benzodiazepine agonists.[53]

Altered Serotonergic System

Alterations in the serotonergic system have been described in human and animal models of HE. CNS levels of serotonin, serotonin receptors, and monoamine oxidases have been found to be increased in human patients with HE.[69] However, the exact role of the inhibitory neurotransmitter serotonin in HE is undefined.

The level of tryptophan, an amino acid precursor of serotonin, is increased in the plasma of human patients with acute liver failure as a result of ammonia detoxification in astrocytes.[12,70] However, a human study examining the relationship between plasma and
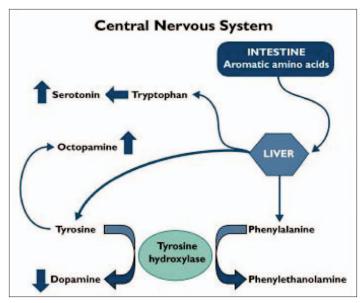

Figure 5. The CNS is overwhelmed by gut-derived aromatic amino acids that have bypassed the dysfunctional liver. As phenylalanine competes with tyrosine for tyrosine hydroxylase, dopamine decreases. Phenylalanine is simultaneously converted to phenylethanolamine, a false neurotransmitter. Tyrosine can be converted to octopamine, another false neurotransmitter. Tryptophan is converted to serotonin, a neuroinhibitor, once it enters the CNS. *Reprinted with permission.*[1]

brain levels of quinolinic acid, a derivative of tryptophan, and the severity of HE did not suggest a major role for this pathway in the pathogenesis of HE.[71]

Altered Amino Acid Metabolism

During liver failure or portosystemic bypass, there is an increase in levels of aromatic amino acids (AAAs), such as phenylalanine, tyrosine, and tryptophan, and a decrease in levels of plasma branched-chain amino acids (BCAAs), such as leucine, valine, and isoleucine[1,3,72,73] (**FIGURE 5**). Normally, the liver removes AAAs efficiently from the portal circulation to keep levels within the systemic circulation low. The brain requires low levels of AAAs, which are the precursors of the excitatory catecholamine neurotransmitters dopamine and norepinephrine. The capacity of normal AAA metabolism in the brain is the rate-limiting step in the formation of excitatory neurotransmitters. High concentrations of AAAs in the brain during HE overwhelm normal AAA metabolism, causing the AAAs to be metabolized via alternative pathways, giving rise to alternative products such as octopamine and phenylethanolamine. These products act as false neurotransmitters, binding to catecholamine receptors but with decreased intrinsic activity, thereby blocking normal catecholamine activation.[3,73] In addition, the conversion of tyrosine to dopamine is depressed in HE, further decreasing catecholamine activation.[3,73]

The BCAAs have a passive role in this pathophysiologic mechanism. BCAAs are decreased in chronic liver disease because they are used as alternative energy sources in muscle and other tissues. BCAAs and AAAs share the same carrier system to enter the brain. A decrease in BCAAs decreases competition for the carrier, thereby allowing more AAAs to enter the CNS.[3,72]

The net effect of an increased level of AAAs in the CNS includes (1) blockage of dopamine and norepinephrine-induced neurotransmission due to a decrease in dopamine and an increase in false neurotransmitters and (2) enhanced production of inhibitory neurotransmitters. The end result is CNS depression. Clinical trials in humans and dogs aimed at correcting imbalances of AAAs and BCAAs have shown conflicting results.[72,74,75]

Manganese Toxicity

The liver is responsible for manganese excretion; therefore, liver disease is associated with elevated blood manganese levels and manganese accumulation within the brain.[30] Dogs with a congenital PSS have significantly increased blood manganese levels compared with healthy dogs and dogs with nonhepatic illnesses.[76] Patients with chronic liver disease have been shown to have manganese deposition in the brain.[77] In the CNS, manganese toxicosis causes Alzheimer type II astrocytosis, reduction in astrocyte glutamate uptake, alteration of glutamatergic and dopaminergic neurotransmission, and impairment of cerebral energy metabolism.[35,45]

Alterations in Miscellaneous Neurotransmitters

Taurine is an inhibitory neurotransmitter that is increased in the brain and cerebrospinal fluid of rodents with experimentally induced acute HE. Plasma levels of taurine have been correlated with the severity of encephalopathy.[78]

Other neurotransmitters that have been implicated in the pathogenesis of HE include opioids,[79] melatonin,[23] methanethiols or mercaptans, and short-chain fatty acids,[12,23,47,70] all of which are derived from bacterial products of gut flora. While many studies support the role of bacterial gut flora in the pathogenesis of HE based on formation of various neurotransmitters, other studies have negated the putative role of these factors, making it difficult to determine their true involvement.[12]

Conclusion

The pathogenesis of HE is best explained as the interaction of many different factors contributing in an interrelated and synergistic manner. A thorough understanding of the various factors contributing to the clinical manifestation of HE is required in order to understand the treatment options recommended for this disease. Type A HE is associated with acute hepatic failure and cerebral edema, which carries a poor prognosis. Practitioners should be prepared to offer their clients referral to a specialty intensive care setting. In human medicine, acute liver failure complicated by HE dictates the need to transfer patients to a liver transplant center. In contrast, types B and C HE may respond dramatically to medical management. Future research may further elucidate the most significant aspects of the pathogenesis of HE, as well as introduce further theories that may contribute to the understanding of the clinical syndrome seen in veterinary patients.

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1. **Which of the following factors is implicated in the pathogenesis of hepatic encephalopathy (HE)?**
   a. increased plasma ammonia concentrations
   b. a reduced concentration of branched-chain amino acids (BCAAs) and an increased concentration of aromatic amino acids (AAAs)
   c. increased levels of benzodiazepine-like substances
   d. manganese accumulation in the CNS
   e. all of the above

2. **Which mechanism does not generate ammonia?**
   a. hepatic metabolism of amino acids
   b. degradation of intestinal protein and urea by urease-producing microorganisms in the colon.
   c. enterocytic metabolism of glutamine.
   d. astrocytic conversion of glutamate into glutamine
   e. muscle tissue catabolism.

3. **Which of the following is not a consequence of hyperammonemia?**
   a. increased permeability of the blood-brain barrier to ammonia
   b. production of reactive oxygen and nitrogen species
   c. astrocyte swelling
   d. decreased cerebral glucose and oxygen metabolism
   e. decreased glutamine formation in astrocytes

4. **The "Trojan horse" hypothesis states that that once ammonia interacts with glutamate in astrocytes to form glutamine, the glutamine enters the mitochondria, where it is converted into**
   a. ammonia and glutamate.
   b. ammonia and tryptophan.
   c. ammonia and urea.
   d. ammonia and GABA.
   e. GABA and dopamine.

5. **Which of the following groups of drugs increase GABA receptor activation and should be avoided in a patient with HE?**
   a. benzodiazepines
   b. barbiturates
   c. neurosteroids
   d. GABA agonists
   e. all of the above

6. **Which of the following statements is false with regard to HE?**
   a. HE in the presence of acute liver failure results in cerebral edema and intracranial hypertension.
   b. Manganese accumulation in the brain causes Alzheimer type II astrocytosis and contributes to clinical signs of HE.
   c. Tryptophan levels are decreased in patients with HE.
   d. Most cases of HE in cats and dogs are due to congenital portosystemic shunts.
   e. Inflammation can exacerbate neurologic signs of HE.

7. **Which of the following is associated with HE resulting from acute liver disease?**
   a. intracranial hypertension
   b. Alzheimer type II astrocytosis
   c. portal hypertension
   d. acquired portosystemic shunts
   e. episodic clinical signs that develop gradually

8. **Which of the following statements regarding inflammation's role in hepatic encephalopathy is false?**
   a. Lipopolysaccharide enhances ammonia-induced changes in cerebral blood flow.
   b. Tumor necrosis factor a and interleukin 6 induce cerebral swelling via production of reactive oxygen species.
   c. Anti-inflammatory agents hold promise for future treatment of HE.
   d. There is a high prevalence of infections and systemic inflammatory response syndrome in patients with liver disease.
   e. The presence of cytokines do not affect blood brain barrier permeability.

9. **Which of the following statements is false?**
   a. The clinical signs associated with stage I HE may only be noticeable to the owner.
   b. Coma is associated with stage IV HE.
   c. Seizures in a dog without other concurrent neurologic signs are typical in HE.
   d. Cats with portosystemic shunts are more likely to have seizures than dogs.
   e. Ammonium biurate crystalluria is associated with congenital portosystemic shunts.

10. **Altered amino acid metabolism caused by liver dysfunction results in**
    a. an increase in BCAAs.
    b. a decrease in AAAs.
    c. an increase in formation of neurotransmitters dopamine and norepinephrine.
    d. a decrease in false neurotransmitters.
    e. central nervous system depression.