Hepatic Encephalopathy in Cats – an Emergency and Critical Care Perspective

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Keywords: Hepatic encephalopathy, hepatic lipidosis, portosystemic shunt, liver failure, hyperammonaemia

1. Overview

1.1 Definition

Hepatic encephalopathy (HE) is the spectrum of neuropsychiatric conditions that occur with liver dysfunction and/or portosystemic shunting, when other brain disease has been excluded.

In human medicine HE is considered either covert, where clinical signs are absent but specific psychometric test results are abnormal, or overt when clinical signs are present. Overt HE is described in cats, but covert HE has not been characterised in veterinary medicine due to inherent diagnostic challenges.

1.2 Aetiology

Human classification schemes are adapted to veterinary medicine which recognise the following aetiologies of HE:

- Type A: acute liver disease in the absence of pre-existing liver disease (for example, toxicity or infectious disease)
- Type B: portosystemic shunt without hepatocellular disease
- Type C: cirrhosis and portal hypertension or acquired portosystemic shunting: may be episodic, persistent, or covert

In cats, the most common causes of hepatic encephalopathy are congenital portosystemic shunts (CPSS), or arginine deficiency secondary to hepatic lipidosis. Recognised toxins associated with acute liver injury in cats include oral benzodiazepines and the anabolic steroid Stanozolol. Liver fluke (*Platynosomum fastosum*) is a parasitic cause of acute liver failure in cats that should be considered in endemic areas.

2. Pathophysiology

Hepatic encephalopathy occurs due to an intracranial imbalance of neurotoxic substances and neuromodulators. The most recognised of these is ammonia. Ammonia (NH_3) is produced in the gastrointestinal tract and the liver manages NH_3 detoxification by both the urea cycle and glutamine synthesis pathways. High concentrations of NH_3 are found in skeletal muscle, so muscle loss can liberate NH_3. While kidneys will most commonly excrete water-soluble urea produced by the liver, there is capacity for NH_3 excretion in hyperammonaemia.

Multiple mechanisms for NH3 inducing neurological signs are proposed. Hyperammonaemia may be excitatory, may increase glutamate release, and may disturb aromatic amino acid transport which can affect serotonin and dopamine synthesis, and impair gamma-aminobutyric acid (GABA)-ergic, serotonergic, and glutaminergic neurotransmission. Ammonia may contribute to astrocyte swelling directly, and secondarily by inducing oxidative stress. It may alter metabolism and energy utilisation in the brain by decreasing adenosine triphosphate (ATP) availability and decreasing microsomal Na+/K+-ATPase.

Elevated manganese levels may also contribute to neurotoxicity by inducing astrocyte swelling, free radical production, and neurosteroid synthesis. Hypermanganesaemia has been demonstrated in dogs with CPSS.

Ammonia and manganese are thought to activate peripheral type benzodiazepine receptors, which increases neurosteroid synthesis and modulates GABA-A receptors to increase GABA-ergic tone.

Amino acid imbalance may also be involved in the development of HE, as increased production of false neurotransmitters may decrease neural excitation. Dogs with HE have decreased ratios of broad chain amino acids to aromatic amino acids.

HE may be precipitated by factors that may affect overall NH3 concentrations or transcellular NH3 shifts including: sepsis/systemic inflammatory response syndrome, gastrointestinal bleeding, constipation, increased dietary protein, hypokalaemia, alkalosis.

Hyponatraemia may compound existing neurological injury, by contributing to osmotic fluid shifts that worsen astrocyte swelling.

3. Clinical Presentation

3.1 Clinical Signs

Common presenting signs of cats with HE include ptyalism, obtundation, ataxia, lethargy, anorexia, and weakness. Clinical signs may be persistent or episodic. Neuroanatomic localisation of neurological signs may be vestibulocerebellar, multifocal, or cerebellar. Neurological progress can be monitored with modified Glasgow Coma Scale scoring.

Tremors have been described in cats with CPSS prior to or after shunt attenuation. They may be generalised or localised (for example, the head or a limb), and are most commonly episodic and non-intentional.

3.2 Differential diagnoses

Hepatic encephalopathy is a metabolic brain disease. Other metabolic encephalopathies recognised in cats with similar presenting clinical signs include hypertensive encephalopathy, hypoglycaemia, kernicterus, thiamine deficiency, uraemic encephalopathy, and non-hepatic hyperammonaemia due to hypocobalaminaemia or renal disease. Importantly, many of these conditions may occur concurrently.

Systemic disease can cause obtundation secondary to poor cerebral perfusion. Other neurodegenerative encephalopathies may present with similar clinical signs.

3.3 Diagnostic findings

A comprehensive physical examination and diagnostic evaluation (including haematology, biochemistry, abdominal and thoracic imaging, and urine analysis) for systemic and metabolic disease is essential. Evaluation of venous blood gas to screen and correct possible precipitating factors is recommended. Advanced imaging (such as abdominal computed tomography) may be required to identify the underlying cause of hepatic dysfunction.

Ammonia concentration, if elevated, confirms hyperammonaemia. However, because clinical signs relate to cerebral intracellular ammonia concentrations, a normal ammonia concentration does not exclude HE.

Pre- and Post-prandial serum bile acids may be elevated with hepatobiliary dysfunction or CPSS.

Magnetic Resonance Imaging (MRI) findings in 3 cats with hepatic encephalopathy identified mild forebrain atrophy (1/3), white matter changes in the centrum semiovale and corona radiata (2/3), and grey matter changes in the cerebellar nuclei (2/3), medial longitudinal fasciculus and reticular formation (1/3). Distributions of MRI lesions may help to differentiate from other metabolic encephalopathies.

It is important to recognise if patients with HE have hepatic failure, and whether there is a concurrent coagulopathy present.

4. Management

Management of HE relies on identification and treatment of the underlying disease process. Any precipitating factors should also be sought and managed. However, patients with moderate to severe HE require initial stabilisation first. The following management strategies should be considered.

4.1 Decreasing ammonia concentrations

Warm water enemas at 10ml/kg q4-6 hours may increase faecal excretion of nitrogenous compounds and reduce colonic bacterial populations and therefore decrease ammonia production.

Non-absorbable disaccharides such as lactulose 1-3ml/10kg body weight PO q6-8 hours (or diluted to 30% as a 30 minute retention enema following warm water enema) is recommended in the management of HE. Its efficacy has been demonstrated in mild-moderate HE in dogs and humans. Proposed mechanisms include colonic trapping of ammonium ions, inhibition of ammonium production by colonic bacteria, encouraging incorporation of ammonium within bacterial proteins, decreased intestinal transit times limiting bacterial ammonia release, and increased faecal excretion of nitrogenous compounds.

Antimicrobials may decrease ammoniogenesis by modifying the gastrointestinal microbial flora. However, importance must be placed on appropriate antimicrobial stewardship. In mild or episodic HE, there is no evidence that concurrent antibiosis is superior to lactulose therapy alone. Rifaximin is the antimicrobial of choice in humans but its efficacy in HE in cats has not been evaluated. Neomycin is no longer preferred as it may impair the efficacy of lactulose and carries a risk of ototoxicity and acute kidney injury. Metronidazole may be

considered but can cause neurotoxicity, which may make clinical progress difficult to assess. Ampicillin 20mg/kg IV q6-8h may be considered and is a low importance antimicrobial. If there is any concern for sepsis or concurrent bacterial infection, appropriate broad-spectrum antimicrobials guided by culture and susceptibilities should be used instead.

Prebiotics/probiotics/synbiotics may modify the microbiota without the negative implications of antimicrobials. A metaanalysis of human literature suggests that probiotics may be useful in covert HE, but there is insufficient evidence that it minimises clinical signs of HE.

Proton Pump Inhibitors should be introduced if there is evidence of gastrointestinal bleeding.

Lipid emulsion has been reported once in a dog with CPSS, suggesting that it may be beneficial as an adjunctive treatment in fulminant HE where other medical management has failed.

4.2 Managing Neurological Signs

Seizure management should be primarily achieved with levetiracetam 60mg/kg bolus, then 20mg/kg IV q8 hours. Benzodiazepines may exacerbate clinical signs of HE and their use is controversial. Phenobarbitone will also increase sedation and undergoes hepatic metabolism so should be avoided in preference of other agents.

Benzodiazepine antagonists have been described in use of a cat that had received multiple doses of diazepam in the management of CPSS associated seizures. The cat had developed worsening neurological signs that improved after administration of flumazenil. However, there is no evidence that flumazenil improves HE signs in the absence of exogenous benzodiazepines.

Intracranial hypertension management may be required in cats with cerebral oedema. Mannitol 0.5g/kg slow IV may be required. Jugular venipuncture should be avoided and 30 degree head elevation may be relevant nursing considerations.

4.3 Airway Management

Severely affected patients may require intubation for airway protection. If intubation is required, consideration should be given to pursuing mechanical ventilation. Not only will mechanical ventilation provide a closed respiratory system with airway humidification and prevent progressive atelectasis, but it allows titration of arterial partial pressures of carbon dioxide and oxygen. This may mitigate the risk of secondary brain injury.

4.4 Additional Supportive therapies

Intravenous fluid therapy should be provided to patients who cannot maintain euhydration by enteral intake alone. An individualised prescription should be considered based on acid base status, with particular consideration to correct alkalosis, hypokalaemia, and safely correct hyponatraemia.

Gastrointestinal therapies including anti-emetic therapies (maropitant 1mg/kg IV q24 hours) should be considered if there are gastrointestinal signs such as vomiting, anorexia.

4.5 Nutrition

As opposed to dogs, protein restriction is not appropriate in cats because they are unable to downregulate protein catabolism. A hepatic prescription diet with moderate levels of a high-quality non-vegetable protein (at least 26%) and adequate arginine and taurine levels is recommended.

Providing enteral nutrition is important in recovery from illness, particularly if hepatic lipidosis is the inciting cause of HE. A recent retrospective study of 48 cats with hepatic lipidosis identified that cats that received rapid reintroduction of nutrition within 12 hours were hospitalised for longer than cats that were stabilised first and had feeding introduced after 12 hours. This suggests while important, initial stabilisation should be prioritised before realimentation. Feeding tubes may be required to achieve nutrition goals.

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