The 5th Annual Vet Education International Online Veterinary Conference

“Feline Hepatic Lipidosis”

With Dr Jane Armstrong
Specialist in Veterinary Internal Medicine

July 2014

Vet Education is proudly supported by Hill’s Pet Nutrition (Australia)
FELINE HEPATIC LIPIDOSIS

P. Jane Armstrong, DVM, MS, MBA, Diplomate ACVIM
University of Minnesota

Introduction

Hepatic lipidosis (HL) is a cholestatic syndrome that develops in cats in association with profound and protracted anorexia, and is the most common form of liver disease in cats in North America. The syndrome occurs worldwide, but there does appear some geographic variation in prevalence. Obese or overweight cats are at increased risk. Most affected cats are middle-aged adults, overlapping the peak prevalence of obesity, but the condition has been reported in cats from 0.5-20 years. There is no gender or breed bias.

Hepatic lipidosis can occur secondary to any disease process that results in marked decrease in appetite (secondary HL). Some of the more commonly associated concurrently diagnosed diseases are pancreatitis, other hepatic disorders such as cholangitis, small intestinal disease, neoplasia, kidney disease, and diabetes mellitus. Concurrent diseases are reported to occur in greater than 95% of HL cases. Hepatic lipidosis occasionally occurs in an otherwise healthy cat that voluntarily (refusal of a new type of food, for example) or involuntarily (such as accidental confinement away from food or overzealous caloric restriction for weight reduction) has severely restricted food intake.

CLINICAL EVALUATION

Physical Examination

Physical examination commonly reveals lethargy, dehydration, and jaundice (about 70% of cases), lethargy, and dehydration. Nonpainful smooth hepatomegaly is common but not always present. Loss of muscle mass despite retention of fat stores can make assigning a BCS difficult. The falciform and inguinal fat pads characteristically are retained and can be seen radiographically and ultrasonographically. Severe electrolyte abnormalities, especially hypokalemia and/or hypophosphatemia, and potentially thiamine deficiency, can result in marked muscle weakness and ventroflexion of the neck. Although spontaneous bleeding is uncommon, bruising or hemorrhage from venipuncture or cystocentesis sites may reflect an underlying coagulopathy. Signs of HE, most notably ptyalism and mental dullness, occur in a minority (<5%) of cases. Clinical findings related to a concurrent disease can be superimposed on the above clinical signs of HL (e.g., weakness, abdominal pain, or mass).

Laboratory Evaluation

The CBC is most commonly within normal limits with primary HL. There may be nonspecific abnormalities such as mild to moderate normocytic, normochromic nonregenerative anemia, poikilocytosis (erythrocytes with an abnormal shape), large numbers of Heinz bodies, lymphopenia, and a mild leukocytosis. Serum biochemical abnormalities in HL are typical of an intrahepatic cholestatic disorder: increased serum bilirubin concentration and increased serum ALP.
activity (most consistent) and increased ALT and AST activities (less common). Although the magnitude of increase in GGT tends to parallel the magnitude of increase in ALP in other forms of liver disease, with HL the GGT tends to be minimally increased or remains within the reference range. Hypokalemia, hypophosphatemia, and/or hypomagnesemia are seen in some cases at presentation or may develop during treatment. Hypoglycemia, hypoalbuminemia, and low BUN occur uncommonly and are indicators of significant altered hepatic dysfunction. The urine of cats with HL commonly reveals bilirubinuria, and lipiduria may be noted in the sediment or during sonographic evaluation. Mild prolongations of coagulation tests, especially prothrombin time, are relatively commonly noted. Response to vitamin K supplementation suggests vitamin K deficiency. Intrahepatic cholestasis leading to reduced enterohepatic circulation of bile acids resulting in reduced absorption of fat-soluble vitamins is the suspected mechanism, rather than hepatocellular failure.

**Imaging and Liver Sampling**

Ultrasonography is the most useful modality available for hepatic imaging and also permits evaluation of other abdominal organs to detect abnormalities associated with diseases that accompany HL. Hepatomegaly is a frequent finding. Diffuse hyperechogenicity of the liver is a characteristic finding with HL; however, it is not pathognomonic and may be seen with other liver diseases and in obese cats or diabetic cats without the clinical syndrome of HL. Although the overall accuracy of ultrasonographic evaluation as the sole criterion for discriminating among categories of diffuse liver disease in cats has been shown to be less than 60% regardless of biochemical or hematologic variables, the exception to this finding was HL. Greater than 70% of HL cases were classified correctly by radiologists in this study.

Liver Cytology and Biopsy

Ultrasonographically guided fine-needle aspiration provides samples that in most cases are adequate for establishing a presumptive diagnosis of HL especially when the index of suspicion is high based on the history, clinical, clinicopathologic, and diagnostic imaging findings. With HL, cytologic examination of the liver reveals cytosolic vacuolization of the majority (80% or more) of sampled hepatocytes. Vacuoles may be large, small, or a mixture of sizes. Aspiration cytology may confirm cytosolic vacuolar change in the liver but may fail to identify other important diagnoses, such as inflammatory or infiltrative disease. An advantage of liver aspiration is that it almost always can be performed without sedation or anesthesia during the initial diagnostic ultrasound and complications are uncommon.

A liver biopsy is not recommended or necessary for all cats with suspected HL. At presentation, many HL cats are not candidates for general anesthesia, which is required for biopsies. Stabilization by correcting fluid, electrolyte, metabolic, and coagulation abnormalities is essential before pursuing general anesthesia. Biopsy confirmation is indicated if the number of inflammatory cells observed
cytologically is judged to be excessive relative to the peripheral neutrophil count or if the cat fails to respond to appropriate nutritional support by showing an approximately 50% reduction in serum bilirubin concentration within about a week of initiation of therapy. If judged to be needed, liver biopsies can be obtained percutaneously with ultrasonographic guidance, laparoscopically, or by laparotomy.

**THERAPY**

Successful recovery of cats with HL initially requires correction of fluid and electrolyte abnormalities but the cornerstone of therapy is enteral nutritional support concentrating on meeting protein and caloric needs. This is often best achieved by inserting a nasoesophageal (NE) tube on the day of admission (see technique below). Depending on patient tolerance and clinical progress, this may be replaced a few days later by either an esophagostomy tube (E-tube) or gastrostomy tube (G-tube) if judged necessary for longer term feeding. An important component of treatment is recognition and concurrent management of any underlying process initially promoting the onset of HL.

**Fluid and electrolyte therapy**

Immediate attention must be given to rehydration therapy and correcting electrolyte imbalances primarily resulting from vomiting and lack of intake. Hypokalemia and hypophosphatemia are important causes of morbidity. Hypokalemia may persist in the face of appropriate supplementation if there is concurrent hypomagnesemia. Magnesium is present in enteral diets in quantities sufficient to normalize serum levels. This is the preferred route of supplementation. Fluid and enteral nutritional therapy should be accompanied by once or twice daily monitoring of serum electrolytes, especially potassium and phosphorus, for the first 3 days, as these may drop precipitously in re-feeding syndrome.

Fluid supplementation with dextrose is contraindicated as cats with HL are intolerant to glucose and such supplementation may exacerbate hyperglycemia. Impaired lactate metabolism is suspected in some cats with HL and is the reason that some authors advise against using lactate-containing fluids, such as Ringer’s. Although a theoretical concern, lactated Ringer’s solution is routinely used with success.

**Enteral feeding**

Enteral feeding must be initiated as early as possible in the course of HL and sustained until voluntary intake resumes. We aim to place an NE tube on day 1 of treatment of any anorexic cat. Force-feeding and appetite stimulants are generally not recommended in cats with HL and are usually reserved for very early or mild cases or for cases with financial constraints where a feeding tube is declined. Although appetite stimulants may increase appetite transiently, they are unreliable for ensuring adequate caloric intake and may encourage a false sense of nutritional support success. Additionally drug metabolism may be impaired in
cats with HL, making dosing and side effects unpredictable. Mirtazapine (1.875 - 3.75 mg per cat q 48-72h PO) is the appetite stimulant of choice of the author because it has both appetite-stimulating and antiemetic effects. A second choice is cyproheptadine (1-2 mg/cat q 12-24 h PO).

An NE tube is inexpensive, does not require anesthesia for placement and uses readily available supplies. However, these tubes require absolute verification of correct placement before feeding and close observation of the cat (+/- use of an Elizabethan collar) to prevent premature removal. Feeding through an NE tube necessitates feeding a liquid diet. Placement of either an E- or a G-tube requires a short anesthesia, which is best delayed until NE feeding has been underway for several days, but either tube type allows the use of a blended solid (canned) food and is sufficiently durable for reliable use in a home environment. Propofol can be safely used in HL cats as an anesthetic agent, such as for placement of a feeding tube. Liquid oral medications may also be administered through any type of feeding tube.

**Diet selection**
Dietary protein is the nutrient that is most efficient at reducing hepatic lipid accumulation in cats in negative energy balance. Protein restriction is contraindicated unless needed in the rare case with hepatic encephalopathy. Carbohydrates are less well tolerated than lipids as a source of calories. Diets that are too high in carbohydrates may cause diarrhea, abdominal cramping, borborygmus, and hyperglycemia. The diet selected to feed a cat with HL should be rich in protein (30 to 40% of metabolizable energy), moderate in lipids (about 50%) and relatively low in carbohydrate (<20%). Suitable commercial liquid diets are Clinicare, EnteralCare™ HLP and FORTOL C+. Recovery formula commercial canned diets are suitable for feeding through E- or G-tubes and have high caloric density, which aids in combating volume intolerance. For feeding via E- or G-tube, Iams Maximum Calorie is preferred by the author due to its high caloric density (2.1 kcal/ml) compared with most other commercial recovery-formula foods, which typically provide about 1 kcal/ml. Canned foods are usually diluted with water (30-90 ml for a 5.5-6 oz can) to achieve a consistency that flows easily through the tube and helps meet patient fluid requirements.

**Refeeding plan**
Nutritional support should aim to deliver 50-60 kcal/kg of body weight/day in most cats. In overweight cats, use estimated optimal weight in calculations to prevent overfeeding. The feeding schedule is determined by the patient’s volume tolerance and the logistics of feeding. Gastric volume in a cat with HL may be dramatically reduced to as little as 10% of its original volume. To minimize vomiting, use a continuous rate infusion or provide small meals with an interval of about 3 hours between meals for the first few days. Decrease to 3-4 meals per day as volume tolerance improves. Each meal must be followed by a low volume water flush. It is often necessary to feed approximately 20% of resting energy requirement (RER) on day 1 (in divided feedings) and then increase the amount by 10-20% every 24 hours until full feeding (RER) is reaching. Fortunately, even
cats that require more time to become volume-tolerant can be expected to show clinical improvement in the first week of therapy. Feeding should be stopped if there is gulping or retching, the meal size reduced by 50% for 12 hours and then increased gradually. It is critical for recovery, however, to continue to feed some food even if vomiting occurs.

**Antiemetic therapy**

Antiemetics often facilitate reintroduction of food. Vomiting can sometimes be reduced by minimizing handling of the cat at the time of feeding and immediately afterwards. Vomiting is a common clinical problem in cats with HL and it often persists during the first week of refeeding despite gradual introduction of increasing meal volumes or use of a CRI. Control of emesis is usually achieved with maropitant citrate (Cerenia, Pfizer) 1 mg/kg q24h SQ or PO. As SQ administration is associated with irritation on injection, maropitant is commonly administered (off-label) intravenously at the same dose and interval. Increasing evidence suggests maropitant also helps provide analgesia for a concurrent painful condition, such as pancreatitis. Metoclopramide (CRI 2-3 mg/kg/day or 0.2-0.5 mg/kg q8h 30 minutes before feeding SQ) is commonly used for its prokinetic effects, even though it is a weak antiemetic in cats. If emesis persists, ondansetron 0.1-1 mg/kg q12-24h IV or PO or dolasetron 0.5 mg/kg q24h IV can also be prescribed. If mirtazapine is used as an appetite stimulant, it also likely has an antiemetic effect. An H2 receptor antagonist (famotidine 0.5-1.0 mg/kg q12-24h IV or PO) is often prescribed non-specifically in vomiting animals to protect the lower esophagus from acid damage.

**Cobalamin therapy**

Evaluation of plasma B12 (cobalamin) concentrations in cats with lipidosis revealed that 40% had subnormal values. Cobalamin deficiency may be severe enough to produce signs such as neck ventroflexion, and anisocoria. The route of choice for supplementation is subcutaneous injection (250 µg/injection once weekly initially for six weeks).

**Treatment of coagulation disorders**

Vitamin K deficiency is frequently suspected in cats with HL. Response to vitamin K suggests that prolongation of coagulation tests is more often the result of impaired vitamin K absorption than decreased factor production. This makes parenteral, rather than oral, supplementation important. If coagulation abnormalities are suspected (or possibly in all cases), administer 3 doses of vitamin K1 (0.5-1.5 mg/kg SQ or IM at 12-hour intervals using a 25 g needle). This treatment is particularly important if a biopsy is to be obtained.

**Other nutrients**

Supplementation with other nutrients has been suggested by some authors but beyond meeting nutritional requirements, benefits to supplement use are poorly documented in the cat. To date, no prospective clinical trials have been conducted to evaluate specific nutrients or supplements in cats with spontaneous
HL. The most commonly prescribed supplements are L-carnitine, taurine, S-adenosylmethionine (SAMe) and silybin (extract from milk thistle). The clinician must consider that prescribing multiple supplements and medications may risk decreasing client compliance with feeding instructions.

L-carnitine is necessary for the transport of long-chain fatty acids into the mitochondria for oxidation and energy production. L-carnitine has been studied in cats during experimental weight gain and loss. L-carnitine helps protect against loss of lean body tissue during weight loss. There is evidence that supplementation with L-carnitine may improve fatty acid oxidation, decrease ketosis, and protect against hepatic lipid accumulation in overweight cats during rapid weight loss. One report, however, failed to show carnitine deficiency in cats with spontaneous HL. Despite this, many clinicians provide L-carnitine to HL cats (250 mg added to the food q12-24h) with the goal of promoting fatty acid oxidation and retention of lean body mass but evidence is lacking that it provides any benefit. A much lower dose (7-14 mg/kg) was used for a protective effect in experimental weight loss studies. To ensure bioavailability, medical grade L-carnitine should be used whenever possible (such as Quinicarin™ Nutramax Laboratories, Inc.; Carnitor®, Sigma-Tau Pharmaceuticals, Inc.).

Taurine is obligatorily used by cats for bile acid conjugation, which increases their water solubility, reduces their cellular toxicity, and facilitates their circulation and renal elimination. Taurine is an essential amino acid for cats, and a small study suggested that cats with HL have low plasma taurine concentrations. Taurine can be supplemented at a dose of 250-500 mg per day in food q24h or divided. Some recovery formula diets are quite high in taurine; for example Hill's a/d provides 132 mg/100 kcal of taurine (caloric density 1.2 kcal/ml). Taurine analysis is not available for many other diets (including Iams Maximum Calorie), suggesting that supplementation may be prudent when this information is not available.

S-adenosylmethionine (SAMe) is an important hepatocellular metabolite and glutathione (GSH) donor with hepatic and systemic antioxidant effects. Low hepatic glutathione concentrations in the liver of cats with HL compared to healthy feline liver is consistent with a reduction in tissue antioxidant availability and provides the rationale to recommend SAMe for treating HL. In healthy cats, orally administered SAMe increases plasma SAMe and liver GSH. The benefit of SAMe or other antioxidants in cats with HL, however, is unproven. The commonly used dosage of SAMe is 35-60 mg/kg PO q24h. Medical grade SAMe (such as Denosyl™, Nutramax Laboratories, Inc.) is recommended. SAMe must be given as an intact tablet on an empty stomach (ideally one hour before feeding) for optimal absorption. Another antioxidant used with hepatic disease is milk thistle or its extract, silymarin. The active isomer silybin is available as silybin-phosphatidylcholine complex which has increased oral bioavailability compared to silymarin. Silybin-phosphatidylcholine is available in combination with SAMe (Denamarin™, Nutramax Laboratories, Inc.).
Prognosis
Cats making a successful clinical recovery from HL demonstrate a gradual reduction in laboratory abnormalities over time. Expect the total bilirubin concentration to decline by > 50% within 7-10 days, even though serum liver enzyme activities may remain close to values documented at the time of case admission. Two important factors affecting the outcome in HL are the presence of a serious, irreversible concurrent disease and how early enteral nutritional support is begun. Absent diagnosis of a fatal underlying condition, recovery rates of 80% or higher can be expected if enteral feeding is initiated early in the course of the disease and sustained until voluntary intake resumes. Cats may need tube feeding for several (3-6) weeks, requiring that the owner is an active participant in their cat’s recovery. Once a cat recovers from HL, recurrence is unlikely.

Selected Readings