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Idiopathic Feline Hepatic Lipidosis

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Introduction

Idiopathic hepatic lipidosis (IHL) of cats is a disease causing severe liver dysfunction; cats afflicted with the disease have a guarded to poor prognosis for recovery. Hepatic lipidosis or fatty liver also occurs in most domestic species including the dog, the chicken, and ruminants. A variety of etiologies for hepatic lipidosis are known and may be classified as either metabolic, nutritional, toxic or hypoxic conditions. The cause of IHL is unknown.

Clinical Findings

The typical signalment of cats diagnosed as having IHL is varied. Early reports suggested older female cats that were obese or had been obese prior to illness were more likely to be affected. A subsequent report showed IHL to occur in both neutered and intact males and females, thin and obese animals, and ages ranging from 9 weeks to 8 years old. Most people believe stressed, anorectic, obese cats are more commonly afflicted, but not all cats of that description develop IHL. Others believe there is probably no age, sex, breed, nutritional state, or body condition predilection to IHL. A possible explanation for this is that there are many possible causes of fatty liver. It is unlikely that IHL has the same etiology in all cases.

The history most commonly accompanying cats with IHL includes a period of profound, total anorexia following a stressful event. Often times, vomiting of clear fluid along with infrequent hard stools or constipation is seen. The cat may also show lethargy and increased salivation.

Physical exam findings, although inconsistent, commonly include weight loss with muscle wasting and sparing of body fat stores relative to what would be expected with anorexia. Jaundice in varying degrees and dehydration are common also. Hepatomegaly, clinical evidence of bleeding disorders, and pale mucous membranes are seen in some cases. Neurologic deficits are seen frequently including weakness, ataxia, depression, intermittent blindness, muscle twitching and coma. These central nervous system signs may be the result of a hepatic encephalopathy due to liver dysfunction. Liver dysfunction in cats with IHL has been shown by increased serum ammonia levels and abnormal ammonia tolerance tests.

Laboratory findings include a nonregenerative, normocytic, normochromic anemia with hypoplastic bone marrow. A stress leukogram may also be seen. Liver enzymes SALT (serum alanine aminotransferase) and SAST (serum aspartate aminotransferase) are elevated and in general, correlate to the degree of hepatic lipidosis and the presence of hepatic cellular membrane disruption. Increases in SALT and SAST are not seen in all cases. SAP (serum alkaline phosphatase) is commonly elevated also. Total serum bilirubin is markedly increased. The ratio of conjugated to unconjugated bilirubin is variable; some authors report higher levels of conjugated bilirubin, while others report that unconjugated bilirubin predominates. Serum triglycerides have been found to be elevated in those cases in which they were measured. Other findings that are consistent with liver failure may include hypoalbuminemia, hypoglycemia, decreased BUN, marked bilirubinuria and a prolonged clotting time.

Post mortem findings may show the liver to be yellow, friable and enlarged, often with rounded borders. There are excessive stores of body fat, muscle wasting and fat infiltration of the bone marrow. Histologic findings of IHL cases have shown varying degrees of lipid accumulation in hepatocytes. However, a distinct fine-vacuolar fatty change is consistent in all cases. The liver lobule may be homogenously involved or affected more in the cen-
Lipid Metabolism

Fatty acids in the body have two major sources, namely diet and peripheral fat lipolysis. An animal's major energy source is from the oxidation of these fatty acids. When fasting, fatty acids constitute almost the entire source of energy. The liver's roles in fatty acid metabolism are: 1) oxidation to generate ketone bodies and energy, 2) to convert excess carbohydrates and amino acids to fatty acids, 3) to release fatty acids from the liver for deposition in adipose tissue and 4) to esterify free fatty acids (FFA) which can form phospholipids or be stored in hepatocytes.

Low levels of insulin associated with low blood glucose levels increase hormone-sensitive lipase which increases lipolysis of peripheral fat stores. Fatty acid release from adipose tissue is also initiated by such hormonal releases of ACTH, TSH, GH, corticosteroids, glucagon, thyroid hormone and the adrenal hormones epinephrine and norepinephrine. These hormones elevate hormone-sensitive lipase in a direct relationship to stimulate lipolysis.

The FFA not oxidized in peripheral tissues are transported bound to albumin to the liver where hepatocyte uptake occurs allowing the FFA to be esterified to triglycerides. Once in the hepatocyte, triglyceride synthesis is dependent on mitochondrial fatty acid oxidation, ketone body formation, endogenous fatty acid synthesis and glycerol precursors.

Very low density lipoproteins (VLDL) are formed by complexing small lipid acceptor molecules called apoproteins with triglycerides with the core made up of triglycerides and a cholesterol ester surrounded by phospholipid, unesterified cholesterol and protein. The availability of apoprotein B, triglyceride, phospholipid and cholesterol, glycosylation of apoproteins and transport of the VLDL from subcellular compartments of hepatocytes to the perisinusoidal space of Disse determine the release of the VLDL into the circulation.

The density of different lipoproteins depends on the amount of protein compared to the amount of triglyceride in them. VLDL are very low in protein and high in triglycerides. VLDL are transported to adipose tissue where, under the influence of lipoprotein lipase, triglycerides are selectively removed and deposited in peripheral adipose stores. This causes the density of the remaining product to increase resulting in a low density lipoprotein.

Pathogenesis of Hepatic Lipidosis

Although there are a variety of causes of hepatic lipidosis in the domestic species, the reason why triglycerides accumulate in hepatocytes is the same; that is, a lipid metabolism defect: the inability of the liver to form lipoproteins and release them into the circulation. The mechanism may involve an excess supply of FFA being presented to the liver, a shortage of cofactors, a hepatic structure defect or a metabolic disorder.

An excess supply of FFA being presented to the liver may result from increased FFA mobilization from adipose tissue. Decreased mitochondrial fatty acid oxidation or decreased apoprotein synthesis result in decreased lipoprotein formation and transport. An imbalance of triglyceride synthesis and secretion of VLDL follows. Normal hepatocytes cannot secrete triglycerides as VLDL as quickly as triglycerides are made from FFA, thus triglycerides accumulate in hepatocytes.

Decreased lipoprotein secretion may be the result of a defect in intracellular transport mechanisms including the inhibition of VLDL transport in the endoplasmic reticulum, impaired secretory vesicle formation and migration or impaired exocytoses of VLDL.

Fatty liver is a common abnormality with and without concurrent hepatic disease, and by itself, a fatty liver has no deleterious effects on hepatic function. Fatty livers in experimental animals do not affect hepatic function. Fatty liver associated with malnutrition likewise, has no deleterious effect on hepatic function. Other evidence shows normal cats can fast for a considerable length of time without the severe problems that anorectic cats which develop IHL have. Not all cats with excessive fat deposits in the liver develop IHL. These facts lead to speculation that a fatty liver may aggrivate or expose an underlying metabolic disease in those animals which develop IHL.

Speculated Causes of IHL

Even though the cause of IHL is unknown, the knowledge of certain nutritional and metabolic requirements of felines has lead to some speculation. Cats require 16-19% of their caloric requirements in protein for maintenance compared to only 4% for an adult dog. They normally have a high rate
of amino acid catabolism. During a fasting period, this rapid protein catabolism may result in marked muscle wasting.

A known nutritional fact of cats is their dietary need for arginine. Cats are unable to synthesize arginine and must rely on muscle catabolism for this essential amino acid during an anorectic period. Arginine is necessary for the conversion of urea cycle in the liver which converts ammonia into urea. An arginine deficiency can lead to hyperammonemia, a contributory factor in the development of hepatonecephalopathy. Arginine deficiency also leads to decreased ornithine and increased carbamoyl phosphate concentrations as alternate metabolic pathways to the urea cycle are used. Carbamoyl phosphate is converted to orotic acid which has been shown to inhibit the conversion of triglycerides into lipoproteins resulting in a fatty liver. Obese cats with a slightly fatty liver already would therefore be more likely affected with a severe fatty accumulation in the liver when an episode of anorexia and muscle catabolism begins. Protein catabolism may also result in decreased apoprotein synthesis contributing to triglyceride buildup in the liver. However, it is not understood why only an occasional anorectic, obese cat is affected with IHL if this mechanism is the true cause.

Another possible cause of IHL is the deficiency of carnitine, a quaternary amine synthesized solely by the liver. Carnitine and associated acyl transferase enzymes play a large role in the transportation of fatty acids into the mitochondria for oxidation to produce energy (adenosine triphosphate). Carnitine deficiency in humans results in lipid accumulation in the liver, heart, muscle and nervous tissue and may lead to death due to hepatic failure. Carnitine deficiency is documented by measuring tissue levels in humans. The condition is treated and responds with oral carnitine supplementation. Similar studies in cats have not been documented.

Diabetes mellitus is a well known cause of fatty liver, but it is usually not the function of IHL. Diabetes mellitus can lead to hepatic failure in cats. Some people believe cats with IHL may have an absolute deficiency of insulin similar to that seen in cats with diabetes mellitus. However, IHL has an insulin deficiency in the face of normoglycemia or mild, prolonged hyperglycemia where as cats with diabetes mellitus have an insulin deficiency with a marked hyperglycemia. A lack of insulin leads to the breakdown of peripheral fat, decreased clearance of plasma lipids and hepatic lipidosis. Insulin deficiency may also be the cause for the fasting hyperglycemia and an abnormal glucose tolerance tests which are sometimes observed in cats with IHL. It is also possible the observed abnormalities in the glucose tolerance tests could be secondary to hepatic failure instead of an insulin deficiency.

Peripheral insulin resistance which produces a relative insulin deficiency may occur in obese cats as it does in obese humans. Elevated serum insulin levels have been shown in cats with a fatty liver. These cats also showed a mild fasting hyperglycemia and abnormal glucose tolerance test similar to the cats with an absolute insulin deficiency. However, one study showed glucose tolerance tests in cats (obese and nonobese) with a fatty liver to have prolonged hyperglycemia with no change in insulin levels. This supports the theory that absolute insulin deficiency rather than insulin resistance is the cause of the glucose intolerance.

If an absolute insulin deficiency is a cause of IHL, serum glucagon must also be deficient or the cat would be diagnosed as having diabetes mellitus. This would explain the mild hyperglycemia or hypoglycemia seen in some cats instead of a severe hyperglycemia. A similar disease in humans involves a somatostatin secreting tumor, but any relationship to IHL is unknown.

Another postulated cause of IHL is a toxic hepatic lipidosis resulting from toxins produced by anaerobic bacteria in the intestinal tract that may be absorbed into the portal circulation and cause necrosis of hepatocytes and impairment of lipoprotein secretion. This is seen in man following a jejunal bypass surgery for obesity where bacteria in the bypassed intestinal segment proliferate. Also bacterial catabolism of nontoxic bile acids into toxic bile acids in the colon may result when excessive bile acids are not absorbed in the ileum. The toxic bile acids may be absorbed into the portal circulation with hepatic damage following. Colonic retention of feces due to constipation may allow absorption of bacterial or other toxic products also. The fatty liver resulting from this condition can be prevented and reversed by treating with metronidazole which controls the bacterial growth.

There are other toxins known to cause hepatic lipidosis including alcohol, numerous drugs including tetracycline, plant toxins, chemicals and aflatoxins. The severity of the clinical signs associated with the fatty liver caused by these conditions apparently depends more on the extent of hepatocellular necrosis than on the presence of fat. Necrosis and hepatic fat infiltration are separate entities. If an agent causes lipidosis by a metabolic pathway, it probably affects adenosine triphosphate concentration in the liver, protein synthesis or lipoprotein output.

Protein-calorie malnutrition is a deficiency of pro-
tein relative to total calorie intake and has been shown to cause hepatic lipidosis in man. This may contribute to the condition in cats because of their high requirement of protein in their total calories for maintenance and a high protein catabolism rate.2,6

Reye’s syndrome is a condition of acute hepatic lipidosis and hepatic encephalopathy in children usually following a respiratory viral infection, a viral-drug interaction or other factors. The cause is unknown, but Reye’s syndrome results in hepatic mitochondrial damage which prevents oxidation of fats leading to hepatic lipidosis. Mortality is about 20%. This syndrome has also been postulated as a cause of IHL.2,4

Other endocrine disorders that can cause hepatic lipidosis include hyperadrenocorticism and hypothyroidism. Animals affected with the latter show some of the clinical signs of IHL including lethargy and anemia. Further study is indicated.1,5

Starvation causes a release of fatty acids from adipose tissue related to lack of blood glucose, sympathetic stimulation and increased growth hormone release. The resulting increase in serum FFA may overload the liver’s ability to process lipids.5,7

**Treatment**

Recovery rates with today’s treatments are only about 10–20%.3 If any attempt at treatment of a cat with IHL is to be successful, early diagnosis and prompt supportive care is necessary.2 Fluid therapy (50-80 ml/kg/day) and caloric energy intake (80-100 kcal/kg/day) are the most important.8 Fluids can be supplied orally or a balanced electrolyte solution can be provided parenterally. Glucose can be added if the cat is hypoglycemic.2,8,9 Body weight should be checked daily.2,8 Caloric intake is only practically given orally, but the cat with IHL is usually anorectic, so force feeding or nasogastric, pharyngostomy or gastrotomy tube feeding may be needed.1,2,6,8 Appetite stimulants in the benzodiazepine class of drugs (Diazepam, Oxazepam, El-fazapam, Chlordiazepoxide) are available and can be tried. Dosages range from 0.2 to 1.0 mg/kg as needed, but generally one to two times per day. These compounds potentiate gamma-aminobutyric acid, a neurotransmitter, which inhibits the satiety center and make the animal feel hungry.2,5,8 In general, a well balanced canned commercial cat food blended into a gruel fed 6-8 times per day in amounts of 5-10 ml/kg via the tube is sufficient. The number of feedings can be decreased while the amount given at one time is gradually increased. Vitamins should be mixed into the gruel. Fat soluble vitamins can be given parenterally to ensure their absorption in severe cases.2,8 If the patient is suffering from a hepatic encephalopathy, a highly digestible low protein diet should be fed. Milk proteins like cottage cheese are excellent because of their high digestibility, and they have a high branched-chain to aromatic amino acid ratio.5,9

However, an adequate supply of protein for apoprotein synthesis and arginine for urea cycle function may be more important than restricting the protein in hepatic encephalopathy cases.6 Oral antibiotics should also be given in cases of hepatic encephalopathy.3,9

Other treatments have been aimed at the insulin deficiency theory with low-doses of insulin given. Some cats have had a return of appetite and resolution of hepatic lipidosis after weeks to months of therapy. However, not all cats respond to insulin therapy and there is risk of hypoglycemia.2,6 If attempted, it should be closely monitored.8

Enemas may be helpful to remove colonic ammonia and bacterial toxins.6 This will prevent further ammonia absorption in the colon. As stated earlier, bacterial toxins may cause hepatic necrosis. Prolonged retention of colonic contents allows absorption of bacterial toxins.5 Metronidazole is also used to control these toxin-producing anaerobic bacteria.2 More research is needed on this subject in cats with IHL.

Some drugs should be avoided when treating IHL. If antibiotics are used, tetracyclines should be avoided since it causes inhibition of the release of lipoproteins in the liver leading to fat deposition.1 Lipotropic compounds like choline and methionine mobilize fat from the liver, but their use in the treatment of IHL is not beneficial.2,6 They are only helpful in hepatic lipidosis caused by the dietary lack of these substances.6,9 Also, excess methionine can exacerbate hepatic encephalopathy.2,6

Glucocorticoids should also be avoided because they enhance protein catabolism and overload the liver with the end-products.2

**Summary**

Fatty liver occurs in most domestic species, but the signs of prolonged anorexia following stress, muscle wasting and retention of body fat stores, nonregenerative anemia, massive fat infiltration of the liver, hepatic encephalopathy and liver failure appear to be a specific syndrome (IHL) suffered by only cats and more likely obese cats.3 However, no evidence has been documented as to one precise cause of this syndrome. IHL must be differentiated from specific disease entities causing similar conditions such as diabetes mellitus, hepatic
lymphosarcoma, cholangiohepatitis, feline leukemia virus induced hepatitis and others. The unique metabolism of cats has lead to some insight into the possible causes of IHL. When these complicated processes are worked out and fully understood, a metabolic derangement may be incriminated as to the cause. A logical and successful treatment will then follow.

REFERENCES


