Feline Hepatic Lipidosis

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KEYWORDS

• Feline • Hepatic lipidosis • Cats • Liver • Triglyceride • Obesity • VLDL • TG

KEY POINTS

- The primary metabolic abnormalities leading to triglyceride (TG) accumulation in the hepatocytes are not yet completely understood.
- The presumptive diagnosis of feline hepatic lipidosis (FHL) is based on patient history, clinical presentation, clinicopathologic findings, and ultrasonographic appearance of the liver; however, history and clinical and clinicopathologic presentation are not specific for lipidosis and any underlying disease process can confound them.
- Nutrition should be initiated on the day of admission to reverse the negative energy balance and catabolic state typical of FHL; early nutrition is the cornerstone of treatment in FHL.

INTRODUCTION

Feline hepatic lipidosis (FHL), the most common hepatobiliary disease in cats,[1–5] is characterized by the accumulation of excessive triglycerides (TGs) in more than 80% of the hepatocytes, resulting in a greater than 50% increase in liver weight,[2,6,7] secondary impairment of liver function, and intrahepatic cholestasis.[2,6,8,9] A specific geographic distribution of the disease has been suggested based on the available reports of FHL from different areas, including North America, Great Britain, Japan, and Western Europe. The higher prevalence of FHL in these areas might be secondary to feeding habits of cat owners and a high incidence of obesity in the feline population.[1]

The pathophysiology of FHL is complex. The primary metabolic abnormalities leading to TG accumulation in the hepatocytes are not yet completely understood, but they could consist of alterations of the pathways of uptake, synthesis, degradation, and secretion of fatty acids (FAs). Nonetheless, the variability in reported historical, physical, and clinicopathologic findings in cats with naturally occurring hepatic lipidosis (HL) suggests that this is a syndrome with many causative factors.

A negative energy balance, usually caused by anorexia, is considered the primary cause for initiating FHL. In an experimental model of FHL, lipidosis occurs within

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2 weeks of the development of anorexia.[8,10] In a clinical setting, FHL has been seen to develop after a period of anorexia that ranges from 2 to 14 days.[1,6] FHL is classified as primary or secondary. In primary FHL, anorexia occurs in a healthy animal secondary to decreased food availability, administration of nonpalatable food,[7,8] or decreased food intake secondary to a stressful event. Secondary lipidosis occurs in animals that develop anorexia as a consequence of underlying disease. Secondary lipidosis is the most common form of lipidosis described, occurring in approximately 95% of cases. The diseases associated with the development of lipidosis are numerous and include diabetes mellitus, pancreatitis, inflammatory hepatobiliary disease, gastrointestinal disease, renal failure, and neoplasia.[1,2]

Because the cat is a pure a carnivore, its lipid and protein metabolism[11–14] make it dependent on obligatory essential FAs (EFAs), amino acids, and vitamins, which become deficient after a period of prolonged anorexia. These deficiencies are considered important cofounding factors for the development of FHL.[2,12]

The development of HL after a period of anorexia has also been described in other strict carnivores, such as the European polecat (*Mustela putorius*) and the American mink (*Neovison vison*).[15,16] The in-depth study of the pathophysiologic mechanisms behind the development of HL in these other obligated carnivores could help better understand the pathophysiology of FHL in cats.

PATHOPHYSIOLOGY

Due to evolutionary pressure, cats have developed unique adaptations of lipid and protein metabolism reflecting a strict carnivorous state,[12–14,17–19] which has an impact on cats' requirements for EFA and essential amino acids.[2,13,20] Like other mammals, cats are unable to synthesize EFAs, like linoleic acid (18:2n-6) and α-linoleic acid (18:3n-3). In addition, unlike other mammals, cats have a limited capacity to synthesize the long-chain polyunsaturated FA (LCPUFA), arachidonic acid (AA) (20:4n-6) from linoleic acid, and eicosapentaenoic acid (20:3n-3) and docosahexaenoic acid (22:6n-3) from α-linoleic acid (18:3n-3). The explanation for this peculiarity is that cats have a severely decreased activity of the enzymes Δ5-desaturase and Δ6-desaturase, enzymes involved in the formation of LCPUFA from EFA.[21–24] Recently, Trevizan and colleagues[11] revealed that cats have an active Δ5-desaturase and that they are able to synthetize AA from γ-linolenic acid via bypassing the Δ6-desaturase step but not in an amount allows them to store this LCPUFA in condition of anorexia.

LCPUFAs are involved in numerous processes. Increased levels of LCPUFAs are well known to protect against the development of HL via the so-called fuel partitioning action of LCPUFA.[25,26] LCPUFAs, n-3 LCPUFA species (ie, docosahexaenoic acid) rather than the n-6 LCPUFA (ie, AA), favor FA oxidation over TG storage and they direct glucose away from FA synthesis by facilitating glycogen synthesis.[27,28] LCPUFAs down-regulate sterol regulatory element binding protein-1 expression and impair its processing, resulting in an inhibition of the transcription of lipogenic and glycolytic genes.[28–30] Furthermore, n-3 LCPUFA species act as ligand activators of the peroxisome proliferator-activated receptor-α (PPAR-α) present in liver and adipose tissue, up-regulating the expression of genes encoding enzymes involved in FA oxidation.[28,31]

Cats possess limited ability to adapt their protein metabolic pathways for conserving nitrogen and they rapidly develop essential amino acid deficiency and protein malnutrition after a period of prolonged anorexia. In both experimentally induced and spontaneous FHL, plasma concentrations of alanine, arginine, citrulline, taurine, and methionine become markedly reduced (>50% reduction from baseline).[2,12,32]