COMMON LIVER DISEASES AND CHRONIC HEPATITIS IN DOGS

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There are many causes of abnormal liver enzymes in the dog. Perhaps the most common cause is a primary non-hepatic condition with secondary liver involvement. There is also a large category of vascular hepatopathies involving the liver and will be discussed under emerging liver conditions. The most important liver disease in dogs to diagnose is chronic hepatitis. Appropriate identification and therapy is often successful.

Reactive Hepatopathies

The so-called “reactive hepatopathies” which occur secondary to non-hepatic disease can result in increased serum biochemical hepatic tests and histomorphologic abnormalities. Most of the reactive hepatopathies cause increases in laboratory tests that evaluate hepatocellular integrity (ALT, AST) and tests of hepatic cholestasis (ALP, GGT). In most cases there are little if any changes in tests that evaluate hepatic function (bilirubin, albumin, glucose, and BUN). Most of the animals with secondary liver disease also retain normal serum bile acid concentrations, which again supports a concept that there is generally minimal hepatocellular dysfunction in most of these disease conditions.

This group is characterized by nonspecific hepatocellular degeneration or necrotic changes without evidence of significant chronic progressive inflammation. Again, these changes are usually secondary to manifestations of a primary non-hepatic disease. The reason the liver often undergoes these changes revolves from the fact that the liver is involved in many metabolic and detoxification functions. Endogenous toxins, anoxia, metabolic changes, nutritional changes and endogenous stress related glucocorticoid release are all examples of conditions responsible for the majority of these changes. Non-specific mild liver changes routinely also occur following general anesthesia.

A good example that helps explain this concept is inflammatory bowel disease in which it is not unusual to observe mild inflammatory changes around portal triads presumed to be the result of abnormal portal uptake of gastrointestinal “toxins”. Throughout the liver and closely associated with portal areas are Kupffer cells (fixed macrophages) that function to filter the blood of injurious toxins, inflammatory mediators and bacteria. When this macrophage system is abnormally insulted Kupffer cells release their own inflammatory mediators that in turn insult the hepatocytes.

Another example could be the sick septic dog having vacuolar change thought to be due to endogenous cortisol release for endogenous stress and hepatic cholestasis from presumed endotoxin or cytokine alteration of bilirubin metabolism.

Histological findings associated with secondary reactive changes include descriptors such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipidosis, intracellular or intrahepatic cholestasis, mild multifocal hepatitis and perportal or variable hepatic necrosis. These changes are devoid of the typical progressive chronic inflammatory cell infiltrates characteristic of chronic hepatitis.

In a review of consecutive liver biopsies at Colorado State University histology grouped as non-specific reactive changes made up the largest category of abnormalities (approximately 25%) In this group we were able to identify an associated disease in many that could explain the likely cause for the hepatic enzyme increases and histological changes observed. Concurrent diseases identified included neoplasia, gastrointestinal, renal, autoimmune, dermatologic, dental, infectious and cardiac disease as a few examples. In some cases an underlying disease is not identified. The ALT values on the average are 1-2 X normal and the ALP values 1-3 X normal. It is interesting to note that in a series of 32 dogs having reactive hepatopathies, 8/8 cases in which serum bile acids were run, all were within the normal reference range again suggesting hepatic function remains intact.

This category appears to be the most common histological change to occur in dogs and is by far the most common cause of elevated liver enzymes. Based on this fact, dogs presented with elevations in ALT and ALP should always have primary non-hepatic disease ruled out first. These changes are usually very reversible and no specific hepatic therapy is required short of treating the primary disease. The liver changes
resolve once the primary etiology is successfully treated. Therapy providing good liver support such as antioxidants may be warranted.

Chronic Hepatitis

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see non-specific mild portal inflammation as a common non-specific reactive change I always ask the pathologist to tell me the severity of inflammation and chronicity of the disease. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis can result with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites and multiple portosystemic collateral veins. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatopencephalopathy. Inflammation in the liver has been given a number of different classifications (ie chronic active hepatitis, cholangiohepatitis etc) but the WSAVA liver standardization group believes we are not able to subclassify hepatitis and suggests we call the condition simply chronic hepatitis. This type of chronic inflammation is uncommon in the cat as their inflammatory disease is directed at bile ducts causing cholangitis.

Etiology. The etiology of this chronic inflammatory condition is generally never determined. Copper associated chronic hepatitis has been documented in a number of breeds as an inherited etiology. The hepatic copper accumulation increases to a level that then becomes toxic to the hepatocyte causing cellular death. The copper accumulation may also result as secondary copper retention from altered biliary copper excretion (see copper associated hepatitis below).

Infectious causes of chronic hepatitis have been associated with leptospirosis and experimental and spontaneous infectious canine hepatitis virus infection. Chronic liver injury has also been reported in dogs with aflatoxicosis and various drug-induced hepatitis. Some dogs treated with anticonvulsant drugs primidone, phenytoin and phenobarbital can develop chronic hepatitis. We have also observed dogs treated with NSAIDs to have hepatitis and there may be a casual relationship in some cases. More commonly however we see acute liver necrosis as a NSAID related drug reaction.

Alpha1-antitrypsin (AAT- also referred to as alpha one protease inhibitor) deficiency in the serum leading to accumulation of AAT in the hepatocytes, is known to cause chronic hepatitis and cirrhosis in man. Investigations by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive. The breed most often associated with AAT accumulation was the cocker spaniel.

Finally immune associated hepatitis may occur in the dog. Circulating autoantibodies are important diagnostic markers used to identify autoimmune liver disease in humans. It appears that autoantibodies (ANA, antimitochondrial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are of a minor importance in classifying canine chronic hepatitis and thought to occur in most cases secondary to the liver damage. Nonetheless, immune-mediated mechanisms are thought to be associated with certain cases of chronic hepatitis and this is supported by the fact that some dogs respond favorably to immunosuppressive therapy.

There is lastly a lobular dissecting hepatitis characterized by a rapid diffuse spread of inflammation throughout the liver lobule. This condition is observed in younger dogs and is associated with hepatic encephalopathy and ascites.

Breed Predisposition. There are a number of breeds that have an increased incidence and suspected genetic basis. Some of these breeds have copper associated chronic hepatitis (discussed below). Other breeds not yet associated with copper include the standard poodle, Cocker spaniel and Scottish terrier. The mechanism of their hepatitis is unknown.

Copper Associated Hepatitis. Abnormal hepatic copper accumulation may be the result of either a primary metabolic defect in copper metabolism or as a secondary event from
abnormal hepatic function altering hepatic copper excretion. When we reviewed a number of dogs having chronic hepatitis not associated with genetic copper accumulation we found many dogs had increases in both copper and iron hepatic concentrations. A number of these dogs were also deficient in hepatic zinc. The interrelationship of the heavy metals and liver disease needs further investigation.

The diagnosis of abnormal Cu accumulation requires a liver biopsy. The measurement of serum copper or ceruloplasmin levels to make the diagnosis. Excess Cu within the liver can be demonstrated using histochemical staining for hepatic Cu using rhodanine or rhubenic acid stain. Definitive determination of excess hepatic Cu requires a quantitative analysis of tissue Cu measured on the biopsy sample. Normal canine hepatic Cu concentrations are less than 400 μg/g (ppm) dry weight liver. Hepatic Cu concentrations in dogs with secondary Cu accumulation generally fall in the range less than 1,000 μg/g dry weight while breed associated hepatotoxicities generally have higher concentrations (>750 μg/g). The location of copper secondary to hepatic cholestasis is generally in zone 1 (periportal) location.

Hepatic copper toxicity was first identified in Bedlington Terriers. It was subsequently shown that affected Bedlington terriers have an inherited autosomal recessive defect, which results in reduced biliary excretion of copper due to hepatic metallothionein sequestration of the metal in hepatic lysosomes. Clinically there is a progressive hepatic Cu accumulation with age ranging from 1,000 to 12,000 μg/g per dry weight of liver. The extent of hepatic damage tends to parallel the increasing hepatic Cu concentrations. In this breed a specific gene has been identified to be responsible for this disease.

During the last decade an increasing number of breeds other than the Bedlington terrier have been linked with concurrent chronic hepatitis and increases in the hepatic Cu content. Liver disease with concurrent Cu accumulation is reported in the Doberman pinscher, West Highland white terrier, Skye terrier, Dalmatian and most recently the Labrador retriever (but not all labs having chronic hepatitis). Occasionally we see other pure breed dogs as well as mixed-breed dogs with high copper concentrations thought to be due to primary copper retention.

Clinical findings. The incidence of chronic hepatitis makes up approximately one fourth of the cases having liver biopsies at Colorado State University (based on a review of 150 consecutive liver biopsies). Chronic hepatitis is more common in female dogs. The average of presentation ranges from 4 to 10 years. It is interesting to note that in both our series and in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs older than 10 years of age. As a general rule old dogs (> 11 years of age) don’t generally present with chronic hepatitis/cirrhosis or if they do they are at or near end stage disease.

The clinical signs parallel the extent of hepatic damage. Early in the disease there are usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease becomes evident. Frequent early signs are gastrointestinal associated with vomiting, diarrhea and poor appetite or anorexia. Ascites, jaundice and hepatic encephalopathy may then occur as the disease progresses. With development of these late signs the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude of rise need not be marked however. One report found 75% of the cases at diagnosis had abnormal bilirubin elevation (mean elevation of 2.6 mg/dl). Serum proteins are variable. As the lesions become more severe albumin levels decline. Serum bile acids are abnormal in most cases having significant chronic hepatitis and measurement of bile acids appear to be a good screening test for the patient with unexplained elevations in ALT and ALP. In our study all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations. In a second study only 8/26 dogs with chronic hepatitis had normal fasting bile acids. However, postprandial samples were not determined in these cases. Determining postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent increases of ALP and ALT values. A definitive diagnosis requires a hepatic biopsy showing characteristic morphological patterns. Needle aspirates are not helpful in making the diagnosis of chronic hepatitis because it is important to see the architecture of the liver and location and extent of the inflammation. One must work with the pathologist when making
the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities found in chronic hepatitis are present

**Prognosis.** There is little information of the prognosis with and without therapy. The prognosis in dogs with advanced chronic hepatitis and cirrhosis is guarded. In a study by Strombeck found mean survivals ranging from 6 to 16 months with therapy. This study also identified that dogs with hypoalbuminemia, hypoglycemia and coagulopathies have very guarded prognostic factors and many died within 1 week of diagnosis. A second study of 79 dogs found that dogs with cirrhosis had a survival of less than one month and dogs with chronic hepatitis had a mean survival in the range of about 20 to 30 months. Most of these dogs were not advanced in their disease and had concurrent corticosteroid treatment. Low albumin, ascites and hepatic encephalopathy are all poor prognostic indicators.

**Therapy.** The management for chronic hepatitis involves removing the primary etiology. Short of treating the primary etiology all other therapies suggested are unproven in the management of chronic hepatitis in dogs. We are still waiting for good clinical studies proving efficacy in treatments. Such studies are hindered even from the start owing to the multiple etiologies of hepatitis and the inconsistent histological descriptions. To date we have only limited case studies and clinical impressions of efficacy in the management of chronic hepatitis.