A Case-based Approach to the Canine Patient with Increased Liver Enzymes (Parts 1 & 2)

Joseph Taboada, DVM, Dipl. ACVIM
School of Veterinary Medicine
Louisiana State University
Baton Rouge, Louisiana

These lectures are interactive case-based presentation in which the audience will work through a series of cases that present for increased liver enzymes, with or without clinical signs. The first case is a young dog that presents for a yearly check-up, the second is an older dog that presents for gastrointestinal signs, and the third is a dog that has gotten into potentially hepatotoxic substances. The sessions will work through the diagnosis and treatment options for these cases. What would you do?

INTRODUCTION

Liver disease is a problem occasionally encountered in older animals with acquired liver disease and younger animals with both acquired and congenital disease. In some instances the underlying problem may have been caused by drug therapy. Many drugs commonly used in older pets have the potential to cause hepatic damage and inflammatory, immune mediated, and neoplastic liver diseases occur more frequently as an animal ages. In cats, hepatic lipidosis is common and inflammatory liver disease can occur singly or in combination with inflammation involving the gastrointestinal tract and/or the pancreas. Liver disease may be acute and resolve with proper management, or it may be a chronic, slowly-developing or waxing and waning condition. In dogs, chronic liver disease tends to progress to an eventual outcome of severe fibrosis or cirrhosis while in cats progressive disease rarely results in the same type of end stage changes. In either case, the disease may affect drug therapy. Managing the underlying disease relies on good supportive measures. There is no “magic bullet” that restores a failing or compromised liver.

The clinical signs associated with liver disease are often vague leading one to suspect potential liver disease for the first time, only when a chemistry panel is evaluated and increased liver enzymes are noted. Unfortunately, increased liver enzymes are not specific for liver
disease; the liver often being affected as an innocent bystander to disease in other organ systems or liver enzymes being increased as an apparently incidental finding, especially in older animals. Metabolic disease such as hyperthyroidism or diabetes mellitus and gastrointestinal diseases such as inflammatory bowel disease and pancreatitis often result in increases in liver enzymes. Diseases resulting in adrenal gland hyperplasia and increases in either glucocorticoids or adrenal androgens also commonly present for increased liver enzymes.

**Suspecting liver disease**

Animals with liver disease usually show nondescript clinical signs such as anorexia, lethargy, weakness, and weight loss. Gastrointestinal signs such as vomiting and diarrhea are common. The signs may be severe in acute disease but tend to develop insidiously in chronic diseases. As chronic liver disease becomes end stage neurologic signs, most often characterized by depressive signs and behavior changes may be noted. Edema, most often noted as ascites, and evidence of bleeding due to coagulopathies may also be seen as liver disease becomes more chronic. In patients with cholestatic liver disease icterus may be noted. Icterus noted on physical exam is often a sign that leads the clinician to consider liver disease early in the evaluation of the older patient.

The most common reason for a veterinarian to suspect liver disease is an increase is liver enzyme activities. A chemistry panel is a common part of the evaluation of older patients as part of routine senior care management, as a preanesthetic screen, or as part of the minimum database for a patient that presents ill. Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or gamma-glutamyltransferase (GGT) activities are common findings. While they may be indicative of liver disease they are not predictive of hepatocellular disfunction. Increased transaminase activities (ALT, AST) are an indication of leakage of the hepatocellular enzymes from the hepatocytes. Increased serum activities may indicate hepatocellular membrane damage, hepatocellular necrosis, or increased hepatocellular enzyme concentration secondary to enzyme induction. Hepatocellular membrane damage is the most common reason for ALT and AST increases and may or may not indicate significant liver disease. It is common for animals with intestinal disease such as inflammatory bowel disease or metabolic diseases such as hyperthyroidism or diabetes mellitus to have increased transaminase activity. A complete drug history is important for patients with increased liver enzyme activities, as many drugs can damage hepatocellular membranes, induce inflammation or necrosis, or induce enzyme production. Questioning the pet owners about
treatment with such drugs as NSAIDs, corticosteroids, anticonvulsants, anthelmintics, antibiotics, imidazole antifungals, and antithyroid drugs is especially important. Increased alkaline phosphatase (ALP) activity may be induced by cholestasis. Increased gamma-glutamyltransferase (GGT) activity represents similar changes. The clinically significant isoenzymes of ALP in cats are hepatic and bone derived. Additionally a corticosteroid-induced isoenzyme (C-ALP) is important in dogs. Pregnant queens may have increased ALP activity due to a placental isoenzyme. These isoenzymes have a half-life of approximately 72 hours in dogs but are significantly less in cats. Disease affecting the liver or biliary tree commonly increases concentrations of the hepatic isoenzyme of ALP. Disease increasing bone turnover increases osseous ALP and the presence of exogenous or endogenous corticosteroids induce increased concentrations of C-ALP in dogs. Even short courses of steroids can cause significant increases in C-ALP activity concentrations that may remain elevated for a month or more after the steroids are discontinued in dogs.

Increased ALP activity is a common finding on the chemistry panel of older dogs. The hepatic isoenzyme becomes increasingly more important as dogs age. When seen without concurrently increased transaminase activity liver disease is probably less likely than steroid influences such as hyperadrenocorticism, exogenous steroid administration, or increased adrenal production of adrenal androgens. Regenerative changes common in older dogs may result in increased ALP activity but other poorly understood derangements of adrenal steroid hormones are increasingly being recognized as causes of ALP activity increase in older dogs. This finding is much less common in cats.

Increased liver enzyme activities alone in a dog without clinical signs or other blood work abnormalities consistent with liver disease should not automatically be considered evidence of significant hepatocellular damage. Increased liver enzyme activities in a cat is a more significant finding and should lead to earlier evaluation but may still not represent significant hepatocellular disease. When increased liver enzyme activities are noted, other parts of the chemistry panel that may become abnormal in animals with hepatocellular disfunction should be scrutinized carefully. Increased bilirubin or decreased albumin in the patient with increased liver enzyme activities should cause the clinician to thoroughly evaluate the patient for liver disease. Decreased BUN or hypoglycemia may be signs of reduced hepatic function but are more commonly noted in young animals with portosystemic vascular anomalies than in older animals with acquired liver disease. If the rest of the chemistry panel is normal and the patient is
otherwise healthy the panel should be repeated in 1 to 3 months. Persistent increases or other
evidence of liver disease should cause the clinician to consider further evaluation.

Increased liver enzyme activities does not necessarily indicate reduced hepatic function
so a test of liver function should be considered as part of the further evaluation of the patient
with suspected liver disease. Fasting and postprandial serum bile acids are the most commonly
used liver function test in dogs and cats. Fasting blood ammonia or ammonia tolerance testing
are liver function tests that are also sensitive and specific. Evaluating blood ammonia is the
preferred test in animals with signs of hepatencephalopathy or in icteric animals where
cholestasis will have an impact on serum bile acid concentrations. Although these tests may
identify loss of hepatic function, they do not correlate well with measurements of drug clearance.

Diagnosing most specific liver diseases is dependent on a tissue diagnosis; a step that
can be invasive and expensive. Hepatic cytology can be used to guide the clinician but cytology
can be misleading when compared to histopathology. It may be useful in infiltrative diseases
such as hepatic lipidosis or neoplasia but is generally less helpful in the diagnosis of
inflammatory and fibrosing conditions or in vascular diseases such as portosystemic shunts.
Because of the higher prevalence of infiltrative diseases in the cat, feline liver diseases lend
themselves to cytologic diagnosis more than canine diseases do.