Indicators of liver disease

Performing a physical examination and a minimum database are the first steps in exploring liver disease.

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Liver disease is a common finding in any veterinary practice, yet the clinical signs may be variable, making it a difficult disease to diagnose and treat. In this series, we discuss approaches to diagnosing liver disease and the challenges associated with treatment. This article covers the clinical signs of liver disease and abnormalities that may be found on a physical examination and minimum database. The second article outlines specific diagnostic tests that can be performed, such as bile acids testing and ultrasonography, when liver disease is suspected. The last article discusses empirical treatment of liver disease that may be helpful in the absence of a definitive diagnosis.

Clinical signs

Pets with liver disease can present with a range of clinical conditions, from severely ill to asymptomatic. Some vague signs can be depression, weight loss, anorexia, vomiting, lethargy, small body stature and poor or unkempt haircoat.[1] Besides these clinical signs, clients may notice acholic feces or other abnormal fecal coloration. More specific signs of liver disease can include icterus (*Figures 1A and 1B,* page 26), ascites, hepatomegaly, microhepatica, coagulopathies and hepatic encephalopathy.

Polyuria (PU) and polydipsia (PD) are also common clinical signs in dogs, but the mechanism for these symptoms is unclear. One hypothesis is that in dogs with portosystemic shunts (PSS) and secondary hepatic encephalopathy that display PU/PD, abnormal neurotransmitters may overstimulate parts of the pituitary gland, leading to adrenocorticotropic hormone release. The end result is an increased antidiuretic hormone (ADH) release from ADH-secreting cells. A higher plasma osmolality is needed to produce antidiuresis, and the urine can become isosthenuric or hyposthenuric but this is highly variable.[2] Other suggested reasons for PU/PD are alteration in portal vein osmoreceptors and potassium depletion.[3] Urinary abnormalities will be discussed in more detail later in this article.

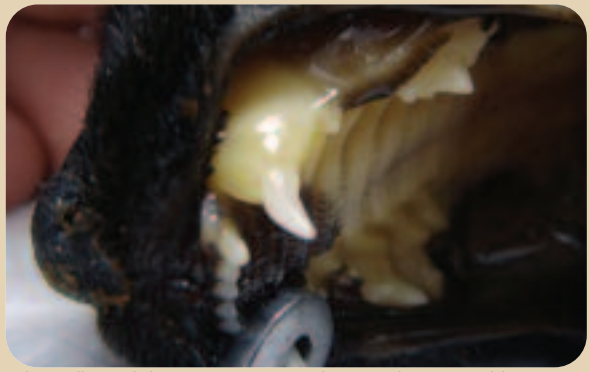
Complete blood count (CBC)

Liver disease can cause several types of

Figure 1A

Jaundice is recognized here by the yellow color to the Pet's ear.

Figure 1B



Jaundice of the mucous membranes is caused by elevated levels of bilirubin.

morphologic abnormalities in the CBC. This is primarily due to changes in either the plasma membrane lipoprotein content or utilization of systemic iron stores. Microcytosis [(MCV-mean corpuscular volume) <60 fl] is a common change noted in dogs with congenital portosystemic shunts and resolves completely after ligation is performed. Microcytosis in cats with congenital PSS is much less common.[4] Microcytosis can also be noted in cases of cirrhosis and idiopathic hepatic lipidosis. Poikilocytes and target cells can be seen in both dogs and cats with hepatic disease. Anemia may be a finding in patients with hepatic disease. A nonregenerative anemia is most commonly found, usually normocytic, normochromic anemia.[5] This anemia is usually associated with inefficient use of systemic iron stores, also known as anemia of chronic disease.[5]

Serum chemistries

Serum biochemical values provide several markers, both direct and indirect, of a possible hepatopathy. Serum hepatic enzyme activities can

Table 1: Causes of Increased Serum Alkaline Phosphate (ALP) and Serum Alanine Aminotransferase (ALT) Levels in Dogs and Cats

Biliary tract abnormalities
- Pancreatitis (ALP/ALT)
- Bile duct neoplasia (ALP)
- Cholelithiasis (ALP)
- Cholecystitis (ALP)
- Ruptured gallbladder (ALP)

Hepatic parenchymal disease
- Cholangiohepatitis (ALP/ALT)
- Chronic hepatitis (dogs) (ALP/ALT)
- Copper storage disease (dogs) (ALP/ALT)
- Cirrhosis or fibrosis (dogs) (ALP/ALT)
- Hepatic neoplasia (ALP/ALT)
- Hepatic lipidosis (cats) (ALP)
- Feline infectious peritonitis (ALP/ALT)
- Toxic hepatitis (ALP/ALT)
- Aflatoxin (ALP)
- Cholangitis (ALT)
- Lymphoma (cats) (ALT)
- Trauma (ALT)

Other disorders
- Diabetes mellitus (ALP/ALT)
- Hyperadrenocorticism (ALP)
- Hyperthyroidism (cats) (ALP/ALT)
- Chronic passive congestion (ALP) (right-side heart failure)
- Diaphragmatic hernia (ALP)
- Septicemia (ALP/ALT)
- Ehrlichiosis (dog)* (ALP)
- Young dog with bone growth (ALP)
- Osteomyelitis* (ALP)
- Latrogenic conditions* (ALP/ALT)
- Anoxia (anemia/shock) (ALT)

NOTE: Almost any disease affecting the liver can cause increased ALP/ALT levels. The conditions above are those that may be more likely to cause a marked increase. However, any of these can occur with minor or no elevation in ALP/ALT values.

*Rarely of importance.

Source: Gastrointestinal, Pancreatic, and Hepatic Disorders, Table 9 and 10. p. 236, 239. Causes of Increased Serum Alkaline Phosphatase Levels. Willard, Tvedten. *Small Animal Clinical Diagnosis* by Laboratory Methods, 4th ed. W.B. Saunders, 2004.

be normal or elevated regardless of the liver's ability to perform normal anabolic and catabolic functions. Liver enzymes can also be normal or below normal during chronic liver disease, cirrhosis for example, as hepatocytes start to die and can no longer make enzymes. The major liver enzymes can be categorized into two main groups: those that are present in the hepatic cytosol, which leak into the blood supply because of elevated concentrations inside the cell or membrane injury; and those that are induced or newly synthesized and released. The following is a brief outline of these enzymes and their possible significance.

The two main enzymes that are associated with cell leakage are alanine aminotransferase (ALT) and aspartate aminotransferase (AST). ALT is the most liver-specific enzyme in the cat and dog.[6] Like most liver enzymes, one can get false elevations due to lipemia and hemolysis. The serum half-life of ALT in dogs with a normal liver is approximately one to two days[7] and enzyme activities peak within two to three days after initial insult.[8] AST is a less specific enzyme than ALT, as there are high levels of AST activity in both skeletal mus-

cle and red blood cells (RBCs). The magnitude of elevation is typically less than that of ALT when there is hepatocellular injury.[6] Elevation of these enzymes may *approximate* the extent of cell injury, but does not indicate reversibility of the injury.[6]

There are two main induction enzymes, alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT). The main reason for elevations in ALP is biliary stasis. Other reasons can include steroid hepatopathy and bone lesions due to isoenzyme elevation (*Table 1,* page 27*)*. Again, false elevations can occur with lipemia and hemolysis. Induction of these enzymes can occur with the administration of drugs such as corticosteroids, barbiturates and anticonvulsants (phenobarbital, phenytoin and primidone) (*Table 2*, page 30). Elevated ALP activity can also be found in young, rapidly growing dogs (less than 15 weeks of age).[8] The serum half-life of ALP is three days in the dog and six hours in the cat.[6] Given the short half-life in cats, minor elevations in ALP can indicate severe hepatobiliary disease and should be investigated. GGT activities tend to follow ALP in most disease processes except hepatic lipidosis in cats. While the ALP activities will become markedly elevated, the GGT activity can remain only mildly elevated or stay within normal limits in cases of hepatic lipidosis.[9]

Total bilirubin concentrations can be an important indicator of hepatic disease, but determining the levels of unconjugated and conjugated bilirubin has little to no value.

The liver is the only site of albumin production in the body, so liver dysfunction can cause hypoalbuminemia.[9] Hypoalbuminemia due to liver disease usually does not occur until greater than 80 percent of liver function is lost. Albumin has a half-life of approximately eight to 10 days in dogs and cats.[9] Diseases such as diffuse necrosis and cirrhosis will typically cause marked deficiencies in serum albumin levels. Portosystemic shunts will also cause hypoalbuminemia, but this is less consistent in cats than in dogs. Before assuming hypoalbuminemia is related to liver dysfunction, one must rule out gastrointestinal or renal disease resulting in protein loss.

Ammonia is created in the intestinal tract by protein and amino acid degradation. Detoxification of ammonia occurs in one of two ways: either the ammonia is consumed in glutamine synthesis, or it is converted into urea in the liver.[9] Because of this, a low blood urea nitrogen (BUN) can indicate a hepatopathy. The clinician must be careful to consider nonhepatic causes of decreased BUN levels. These can include prolonged restriction of protein intake through either therapeutic diets or total anorexia.[5,9]

Bilirubin is typically formed from the breakdown products of RBCs or other heme proteins. In the liver's Kupffer cells, RBCs are degraded to free hemoglobin and these cells then phagocytose circulating hemoglobin.[6] The hemoglobin is then converted to bilirubin. This lipid-soluble form of bilirubin crosses the cell membrane and enters the circulation at which point it is bound to albumin. This unconjugated form of bilirubin is then taken up by hepatocytes. Failure of this mechanism leads to the formation of unconjugated hyperbilirubinemia. In hepatocellular disease, bilirubin uptake, conjugation and excretion are usually impaired. Total bilirubin concentrations can be an important indicator of hepatic disease, but

TABLE 2: Effects of Drugs on Liver Disease

Drugs That Have Been Known or Thought to Cause Increased Alanine Aminotransferase (ALT) Activities

Anti-epileptics
Phenobarbital (important)
Phenytoin
Primidone (important)
Anti-inflammatories
Acetaminophen (important) especially cats
Carprofen
Glucocorticoids
Ibuprofen
Phenylbutazone
Salicylates
Antimicrobials
Doxycycline
Erythromycin
Griseofulvin
Itraconazole
Ketoconazole
Mebendazole
Nitrofurantoin
Oxacillin
Sulfasalazine
Sulfonamides
Tetracycline
Thiacetarsemide (important)
Trimethoprim-sulfa (important)
Chemotherapy/ Immunotherapy
Azathioprine
L-Asparaginase
6-Mercaptopurine
Methotrexate
Miscellaneous medications
Amiodarone
Methimazole
Quinidine
Sedatives/anesthetics
Barbiturates (important)
Diazepam
Halothane
Methoxyflurane

Note: These medications do not necessarily cause hepatic disease. In a patient with elevated ALT that is given one of these medications, the ALT should be rechecked two to four weeks later after the medication is stopped. Those medications that most likely elevate ALT are marked (important). The other medications may still cause severe hepatic disease.

Source: Willard M, Tvedten H, Turnwald, G. *Small Animal Clinical Diagnosis by Laboratory Methods.* W.B. Saunders. 4th ed, 2004: p. 232.

Drugs That Have Been Known or Thought to Cause Cholestasis or Hepatic Enzyme Induction Resulting in Increased Serum Alkaline Phosphatase (ALP) Activities

Anti-epileptics
Phenobarbital (important)
Phenytoin
Primidone (important)
Anti-inflammatories
Glucocorticoids
Ibuprofen
Phenylbutazone
Salicylates
Antimicrobials
Cephalosporins
Erythromycin
Griseofulvin
Nitrofurantoin
Oxacillin
Tetracyclines
Thiabendazole
Trimethoprim-sulfa
Chemotherapy/ immunotherapy
Asparaginase
Azathioprine
Cyclophosphamide
Dapsone
6-Mercaptopurine
Methotrexate
Miscellaneous medications
Anabolic steroids/androgens
Estrogens
Gold salts
Methimazole
Progesterone
Sulfur
Testosterone
Vitamin A
Sedatives/anesthetics
Barbiturates (important)
Halothane
Phenothiazines

Note: Medications that are most likely to elevate ALP are marked (important). The other medications may or may not cause an elevation.

determining the levels of unconjugated and conjugated bilirubin has little to no value.

Before assuming bilirubin levels are elevated because of liver disease, hemolytic processes must be ruled out. RBC counts, as well as the presence of spherocytes, target cells and nucleated red blood cells are good indicators of a hemolytic process.

Hemolysis in blood samples can also falsely elevate total bilirubin concentrations. True bilirubin elevations indicate severe hepatic dysfunction because the liver's reserve capacity for bilirubin processing is 30 times the typical bilirubin levels. Jaundice can be noted at two to three times normal total bilirubin levels, where icteric serum and bilirubinuria can be detected at 0.6 to 1.0 mg/dl.[6]

Hyperglycemia can be a secondary effect of feline hepatobiliary disease, but this may be stress-related and not directly caused by hepatic disease.

Serum cholesterol levels can be markedly decreased in patients with congenital or acquired portosystemic shunts or fulminant hepatic failure.[8] The mechanism of hypocholesterolemia in portosystemic shunts is unknown but may be related to decreased cholesterol synthesis or increased incorporation of cholesterol into bile acids. Hypercholesterolemia can be noted in severe intrahepatic cholestasis or posthepatic obstruction of the bile duct, especially in the cat.[5,8] This increase is due to the decreased biliary excretion of cholesterol.

Glucose regulation is an important function of the liver that is compromised once 70 to 80 percent of liver function is lost.[5] Hypoglycemia is a rare complication of end-stage chronic inflammatory disease but occurs more often in acute fulminant hepatic failure or portosystemic shunts in small breed dogs. Hypoglycemia occurs due to decreased hepatic glucose production and depleted hepatic glycogen stores. Hyperglycemia can be a secondary effect of feline hepatobiliary disease, but this may be stress-related and not directly caused by hepatic disease.

With liver disease, electrolyte imbalances can occur due to vomiting, diarrhea and anorexia secondary to hepatobiliary disease. The most common electrolyte abnormality is hypokalemia, due to renal or gastrointestinal losses, reduced intake and secondary hyperaldosteronism.[10] For this reason, supportive care, fluid therapy, electrolyte replacement and antiemetic therapy during hepatic crisis are necessary.

Urinalysis

While the serum chemistry results will generally reflect most abnormalities associated with liver disease, the urinalysis can also be affected.

Clinical signs such as PU/PD may be confirmed with evidence of unconcentrated urine, often being in the isosthenuric range.

Elevated urine bilirubin levels can suggest liver disease, especially in the cat. Conjugated bilirubin is water-soluble and excreted by the kidneys. It is normal to see mild to moderate levels of bilirubinuria in concentrated canine urine, because dogs have a very low renal threshold for bilirubin excretion.[6] Cats have a high threshold for bilirubin excretion and any amount of bilirubin in the urine is significant and an indicator of a disease process.

Crystalluria is another fairly common sign of liver disease, especially in dogs. In patients with portosystemic shunts, 40 percent to 75 percent of dogs and 15 percent of cats will develop ammonia biurate crystals in the urine.[5] Those crystals develop because of a deficiency in hepatic urate oxidase leading to hyperuricemia. If there are elevated levels of urine ammonia concurrently, biurate crystals will form. These crystals can develop into uroliths and cause hematuria and pyuria.

Conclusion

In patients with liver disease, the physical examination and history findings can suggest that diagnostic testing is warranted. Bloodwork and a urinalysis can assist in narrowing down the rule-outs but they cannot tell us what, specifically, is ailing the patient. Also, most of these laboratory tests can be confounded by sampling error (lipemia, hemolysis), isoenzyme detection, or extrahepatic causes. Therefore, after obtaining a minimum database reflecting some of these abnormalities, further testing is indicated. Specific liver function tests such as fasting and postprandial-bile acids testing can help determine if liver function is compromised. Abdominal ultrasonography can be used to locate a focal mass or diffuse change within the liver. Ultrasound can also assist in obtaining a liver biopsy. These and other tests will be discussed in the following articles.

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