Hepatopathy Headache: Evaluating the Asymptomatic Patient

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Patients with significant hepatobiliary disease can have normal test results and conversely healthy patients can have abnormal test results. This lecture will focus on asymptomatic patients with elevated liver enzymes as it can be difficult to know how to proceed when a patient presents with abnormal liver enzymes but no clinical signs.

Markers of hepatocellular damage: alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

ALT is found in high concentrations within the cytoplasm and mitochondria of hepatocytes. It is considered the best marker for hepatocellular injury in dogs and cats. ALT activity is relatively liver specific but can occasionally be increased due to muscle injury. Correlation with serum creatinine kinase activity is useful for differentiating ALT of muscle or hepatic origin. Serum levels depend on both the number of hepatocytes affected and the severity of injury but do not correlate with reversibility of injury or hepatic function. For instance, an acute severe injury can cause markedly high enzyme activity, but may be mostly reversible without signs of liver dysfunction. On the other hand, end-stage liver disease may only have slight increases in enzyme activity because of a marked decrease in the number of hepatocytes. Judging the magnitude of a change in serum enzyme values can be challenging. As a rule of thumb, a 2-3 fold increase above the reference interval is generally considered mild, where as a 4-5 fold increase is moderate, and as the value reaches closer to a 10 fold increase this is considered marked. Inflammatory or necrotizing disorders are generally associated with the largest increases (of the leakage enzymes). Serum or plasma ALT activity has been reported to have a half-life of about 40 to 61 hours in dogs and 3.5 hours in cats.

AST is also a marker of hepatocellular damage. This enzyme is present in significant quantities in skeletal muscle, brain, liver, kidney, erythrocytes, and cardiac tissue. Muscle damage and hemolysis can cause considerable increases in AST activity. AST is considered a less liver specific than ALT. The causes of an increased AST activity are similar to those of ALT. AST has a half-life of approximately 12 hours in dogs and 1.5 hours in cats

Markers of cholestasis: Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT)

ALP is associated with the cell membrane in many tissues, including hepatocytes. Only liver and bone ALP in both cats and dogs and corticosteroid-induced ALP in the dog only, contribute significantly to serum activity. An elevated serum ALP activity can indicate primary hepatobiliary disease (ie cholestaisis), canalicular cell necrosis, or alternatively

increased hepatic synthesis. ALP is considered a sensitive marker for cholestasis. An elevated serum ALP activity does not distinguish between intrahepatic and extrahepatic cholestasis. A wide variety of diseases can cause intrahepatic cholestasis through hepatocyte swelling, leading to obstruction of small bile canaliculi and extrahepatic cholestasis. An increase in the serum ALP activity can be induced by endogenous, topical or systemic glucocorticoids, anticonvulsant medications, and possibly other drugs or herbs. ALP activity measurement has a high sensitivity (80%) for hepatobiliary disease, but its specificity is low (51%). The serum half-life of liver ALP is approximately 70 hours in the dog and 6 hours in the cat.

GGT is a membrane-bound enzyme found in biliary epithelial cells and hepatocytes. It is also found in pancreatic, renal tubular, and mammary gland epithelial cells. Elevations are usually caused by cholestasis or biliary hyperplasia resulting in enzyme induction. GGT may be a more sensitive indicator of hepatobiliary disease in cats than ALP, owing to the shorter half-life of ALP in cats. A notable exception is hepatic lipidosis, as moderate to marked increases of ALP are often seen with no to minimal increases in GGT. In dogs, it is thought to be less sensitive, but more specific, for liver damage than ALP. Corticosteroid administration and hyperadrenocortiscm can cause increased serum GGT activity in dogs, likely due to enzyme induction, but serum GGT is less influenced than ALP by enzyme-inducing drugs. Phenobarbitol can cause a transient increase in GGT. GGT has a half-life of approximately 72 hours in dogs

Tests of Liver Function:

1. Markers of hepatic synthetic function:
On the chemistry panel, it is important to assess the liver functional parameters which include bilirubin, albumin, glucose, BUN, and cholesterol. A reduction of approximately 70% to 80% of hepatic function must be present before a decrease in BUN, cholesterol, glucose and albumin are observed. Therefore these abnormalities are not considered sensitive indicators for the diagnosis of hepatobiliary disease. Also, changes in these analytes also occur due to many other non-hepatic diseases.

2. Bile Acids:
The most sensitive function test available are serum bile acids. Increases in fasting or postprandial serum bile acids concentrations are consistent with hepatic dysfunction, portosystemic shunting, or cholestasis. Bile acids should NOT be run in patients with an elevated bilirubin concentration. Bile acid concentrations >25-30 µmol/L in dogs and > 25 µmol/L in cats are suggestive of hepatobiliary disease, i.e. decreased functional mass, alterations in portal circulation. It is important to note that increases in bile acids have also been documented with tracheal collapse, gastrointestinal disease, and hyperadrenocortism. Most animals with congenital or acquired portosystemic shunting have markedly increased post-prandial bile acids concentrations, typically > 100 umol/L.

3. Ammonia:
Ammonia is not commonly performed in patients with suspected liver disease as it is not very stable in plasma samples, therefore an in-house analyzer is needed to reliably measure ammonia. Elevations in serum ammonia generally are associated with hepatic encephalopathy. Ammonia elevations best reflect portosystemic shunting rather than direct parenchymal damage as it has been suggested that a greater than 70% reduction of hepatic function is required for serum ammonia concentration to be increased.

Work-Up: General Guidelines

In an asymptomatic patient with increased liver enzymes, the value should be confirmed at least once. Once confirmed, the next step is a careful history to exclude drug/toxin associated enzymes elevations (see list below) or signs that may indicate an extrahepatic cause such as cushing's (dog), hyperthyroidism (cat), etc as a possibility. Additionally, a CBC, full chemistry panel, and urinalysis +/- total T4 should also be performed to look for other hints that may indicate the underlying cause of the hepatopathy such as microcytosis seen with some portovascular anomalies, glucosuria in some dogs with copper storage hepatopathy, etc.

If no likely cause for the elevation in liver enzymes can be found, such as drug induced or extrahepatic disease, there are two paths one could go down: 1) recheck liver enzymes in ~ 4 weeks or 2) begin a further diagnostic evaluation (abdominal ultrasound and/or bile acids testing). As a general rule if there is persistently elevated liver enzyme activity, I typically begin with an abdominal ultrasound followed by bile acids testing unless I am primarily concerned with a congenital portosystemic anomaly, in which case I lean toward a bile acids test as my initial diagnostic.

Imaging:
Routine abdominal radiographs are helpful in determining liver size and shape. An abdominal ultrasound is noninvasive, readily available and is the most informative initial imaging modality for liver disease. It is most valuable for assessing for hepatic masses, vascular anomalies, and diffuse change in the liver parenchyma. It is important to note that a sonographically normal liver does not rule out significant hepatic disease or even a hepatic mass. A study in 2013, found that 64% of sonographically unremarkable livers had histologic abnormalities. Ultrasound is also very useful for evaluation of the gallbladder and biliary tree. Gallbladder mucoceles, choleycystitis, choleliths, and intrahepatic or extrahepatic bile duct dilatation can be identified.

Sonographic abnormalities of the liver or of the gallbladder may warrant a fine need aspiration for cytological evaluation or percutaneous ultrasound-guided cholecystocentesis for cytological evaluation and culture. Primarily, I use cytological evaluation in an asymptomatic patient to assess for cancer in the liver and infection in the biliary tree. It is not useful for diagnosing inflammatory disease in the liver.

If the ultrasound is normal, then I assess the following factors to determine if more of a diagnostic evaluation is needed. 1) Signalment of the patient, 2) Enzyme pattern (cholestatic vs leakage vs mixed), 3) severity and duration of elevation, 4) abnormal functional testing.

1. Signalment: Signalment may be helpful since several breed-associated hepatopathies and portosystemic vascular anomalies have strong breed associations. If I find an elevated ALT in these patients, I am more inclined to recommend a further diagnostic workup rather than ongoing monitoring or trial with empirical therapy.

Copper-associated chronic hepatitis: Bedlington terriers, Labrador retriever, Dobermans, Skye terriers, West Highland white terriers, American/English Cocker Spaniels, English Springer Spaniels, Dalmatians, Siamese and European shorthairs

Idiopathic chronic hepatitis: Doberman pinchers, Cocker spaniels, Standard Poodles

Congenital portosystemic anomalies:
Intrahepatic Shunts: Maltese terriers, Yorkshire terriers, Havanese terriers, Pugs, Miniature schnauzers
Extrahepatic shunts: Irish wolfhound, Retrievers, Australian cattle dog, Austrailian Shepherd
Portal vein hypoplasia (formerly referred to as microvascular dysplasia): Miniature poodles, Yorkshire terriers, Maltese terriers (similar breeds to intrahepatic shunts)

Lobular Dissecting Hepatitis: Standarad poodles, American Cocker Spaniels

Gallbladder mucoceles: Shetland sheepdogs, cocker spaniels

2. Enzyme pattern, severity and duration of enzyme elevation(s), and functional testing results
Further diagnostic testing is also indicated if the patient in question is not of a breed predisposed to a hepatopathy, has no history of drug exposure, and has any of the following: 1) An elevation of greater than three times the upper reference range limit in ALT that is repeatable at least once, 2) progressive increase in enzyme activities, 3) single enzyme activity elevation with concurrent increase in bilirubin or decreased albumin concentration, 4) elevated bile acids. It is also warranted to further evaluate mild chronic elevations of any single enzyme.

General guidelines for increases in ALT activity or ALT>> ALP:
As stated above, the next diagnostic work up for an elevated ALT includes an abdominal ultrasound and bile acids testing. It is important to note that both of these tests can be normal despite liver disease being present. If abdominal ultrasound and bile acids are normal, the next step is either a liver biopsy or treatment trials with hepatoprotectants or antibiotics. In cats, I lean toward an antibiotic trial over hepatoprotectants with either

clavamox OR marbofloxacin and metronidazole for possible bacterial cholangitis. In dogs, I usually lean toward a hepatoprotectant trial unless the ultrasound showed gallbladder sludge or cholecystitis. ALT values should then be rechecked ~2 weeks later (while still on antibiotic if trial was antibiotics was elected). If there is improvement, ongoing therapy is recommended for a total of 4-6 additional weeks. If values remain persistently elevated a liver biopsy is recommended.

General guidelines for solitary ALP elevation or ALP >>ALT elevations:
A common finding is an elevated ALP in an asymptomatic dog (uncommon in cats). If there are clinical signs such as polyuria, polydipsia, polyphagia, consider testing for hyperadrenocortism and examining for exogenous sources of steroid administration. If completely asymptomatic, the most likely causes include early gallbladder mucocele, nodular hyperplasia, idiopathic vacuolar hepatopathy, and hepatic neoplasia. The next step in these patients with persistently elevated ALP elevation is an abdominal ultrasound. If abdominal ultrasound is unremarkable, most of the time I will benign neglect these patients but will periodically monitor for large jumps in the ALP values (ie: jump from 800 to 3500) which would prompt me to repeat an abdominal ultrasound. I suspect that many of these dogs have idiopathic vacuolar hepatopathy.

Liver Biopsy
A biopsy is required for a definitive determination of the nature and extent of hepatic damage and to appropriately direct the course of treatment. The commonly used liver biopsy techniques in dogs and cats are percutaneous needle biopsy, laparoscopic liver biopsy, and surgical liver biopsy. Each has advantages and disadvantages. Generally speaking, surgical or laproscopic liver biopsies are preferred to tru-cut liver biopsies.

COMMON CAUSES OF ELEVATED HEPATIC ENZYME ACTIVITIES IN ASYMPTOMATIC DOGS AND CATS:

There are other causes of elevated liver enzymes in both symptomatic and asymptomatic patients that are not described below. In addition, it is important to note that not all of the patients with the disease processes described below are asymptomatic.

Reactive hepatopathies:
Reactive hepatopathies occur secondary to a primary disease process elsewhere in the body, often involving the splanchnic circulation, that damage the liver. Commonly the ALT and ALP are mild (<3 x elevated) and functional testing is normal. In these cases, histopathologic changes include inflammatory changes limited to the portal areas and are not accompanied by fibrosis or hepatocyte necrosis/apoptosis. In this case the liver lesions do not represent the primary problem and one should search for an extra-hepatic cause. A common culprit is gastrointestinal disease. Therapies that could be attempted include, diet change to novel protein or hypoallergenic diet or probiotic therapy.

Drug induced injury:
Drug-induced liver injury: includes but not limited to, acetaminophen, tetracycline, doxycycline, methimazole, doxycycline, anesthetic agents, arsenical compounds, carprofen, diazepam/oxazepam, griseofulvin, itraconazole, ketoconazole, lomustine, phenobarbital, phenytoin, primidone, mebendazole, methimazole, oxibendazole-diethylcarbamazine, tetracycline, clindamycin, nitrofurantoin, trimethoprim- sulfadiazine, azathioprine.
Drug associated ALP induction: herbal medications, phenobarbital or glucocorticoids.

Vacuolar hepatopathy (VH):
Hepatic vacuolar change is a common histological diagnosis in dogs, but not cats. VH in dogs is most often associated with hyperadrenocorticism (HAC). Other causes include congenital glycogen storage disorders, breed-specific disorders, hepatic nodular hyperplasia, and a variety of stress-associated secondary diseases. There is a subset of dogs that do not have an underlying disease leading to VH and these dogs are referred to idiopathic vacuolar hepatopathy. Scottish Terriers are reported to have a breed-specific syndrome associated with VH and elevated ALP. Most dogs are middle-aged to older. There does not appear to be a breed or sex predisposition other than in the Scottish terrier. I personally do not treat dogs with idiopathic vacuolar hepatopathy. There is no evidence that hepatoprotectants such SAMe or silamyrin are beneficial for this syndrome.

Congenital portosytemic vascular anomalies:
These include microscopic (portal vein hypoplasia/microvascular dysplasia) and macroscopic (congenital extrahepatic, intrahepatic portosystemic shunts, arteriovenous malformation) defects in vascular development. Clinical signs are directly related to the degree of diversion of portal blood flow around the liver, so patients with vascular anomalies may be asymptomatic in cases of mild shunting.

Hepatic Nodular Hyperplasia (dogs, not cats):
This is a benign process causing an increase in liver enzymes and histological changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes. Liver function remains unchanged. The etiology is unknown but appears to be an aging change in dogs; most of those affected are greater than 10 years of age. Laboratory findings include an ALP increase (mean ALP ~600 IU/L), but some may have mild increases in ALT and AST concentrations. Ultrasound may be normal or may demonstrate larger nodules (many can be only microscopic and not observed on ultrasound). Biopsy confirms the diagnosis. No specific therapy is needed.

Cholangitis:
Inflammatory bile duct diseases are among the most common types of hepatopathy in cats. While many of these cats present ill, there is a subset that are largely asymptomatic. Feline cholangitis may be accompanied by pancreatitis, inflammatory bowel disease and cholecystitis. The two forms of cholangitis commonly encountered are neutrophilic

(infectious) cholangitis and lymphocytic (immune mediated) cholangitis. Biopsy is required to confirm the diagnosis of inflammatory cholangitis.

Bacterial cholangitis and cholecystitis (dogs and cats):
Bacterial cholangitis/cholecystitis is usually caused by an ascending bacterial infection from the gut, however hematogenous spread can also occur. Common bacterial isolates include E. coli, Enterococcus spp., Streptococcus spp., Clostridium spp. Aerobic and anaerobic culture of the bile is recommended in a patients undergoing further evaluation of elevated liver enzymes. Bacterial cholangitis can be diagnosed via percutaneous ultrasound-guided cholecystocentesis. The bile should be submitted for cytology and aerobic and anaerobic cultures. Treatment usually requires at least 4-6 weeks of appropriate antibiotic therapy.

Chronic hepatitis:
Common causes are copper storage (dogs >>>> cats) and immune mediated hepatitis. Infectious etiologies are an uncommon cause of chronic hepatitis, however if histopathology showed pyogranulomatous hepatitis a work up for an infectious agent should be pursued.

Hepatic tumors:
These can be primary or metastaic. Primary hepatic neoplasms are less common than metastatic neoplasms. Hepatocellular adenomas are common in dogs and are generally restricted to a single liver lobe. These tumors are very slow growing and do not metastasize. Hepatocellular carcinomas (HCC) are the most common primary liver tumor in dogs and second most common primary liver tumor in cats. These are malignant tumors that can be carry a good prognosis when they are comprised of a single large tumor and surgically resectable. HCC that are nodular or diffuse, carry a poor prognosis. The liver can also be involved in other malignant processes including malignant histiocytosis, lymphoma, and systemic mastocytosis.

In cats, neoplasms of the biliary system (bile duct adenocarcinomas) occur more frequently than neoplasms of hepatic cell origin. Lymphoma and mast cell neoplasia occur relatively frequently as well.

In summary:
Abnormal liver enzymes in asymptomatic patient that are persistent and can't be attributed to an extrahepatic cause, should be further investigated. Ultimately, a liver biopsy is required for most patients to obtain a definitive diagnosis. If financial constraints limit a further workup, trials with hepatoprotectant therapy or antibiotic therapy can be trialed.

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