



Common inflammatory liver diseases in the dog (part 1)

The pathogenesis, clinical signs and diagnosis of common inflammatory liver diseases in dogs, is outlined by Daniel Davies BVMedSci (Hons) BVM BVS (Hons) MRCVS, resident in small animal diagnostic imaging, University College Dublin

SYNOPSIS

The most common causes of inflammatory liver disease in dogs include non-specific reactive hepatitis, chronic hepatitis (CH) and acute hepatitis (AH). Other common causes of hepatic disease in dogs include neoplasia, vascular anomalies (ie. portosystemic shunts) and biliary tract disorders. Diagnosis of canine hepatic disease often involves a combination of history taking, clinical examination, evaluation of clinical pathology data, diagnostic imaging, and will often require the histological evaluation of representative liver biopsies. Once a diagnosis has been achieved, management of canine hepatic disease needs to be tailored to each patient's condition in order to maximise the benefit of treatment, and also to reduce the risk of potentially life threatening complications arising as a result of therapy. This is the first of two articles on the topic of inflammatory liver disease in dogs. This article will briefly summarise the most common canine inflammatory hepatic conditions (non-specific reactive hepatitis, acute hepatitis and chronic hepatitis) seen in first opinion practice, discuss clinical signs and diagnostic investigation. The second article in this series will discuss the management of these conditions.

INTRODUCTION

Parenchymal liver disease may be divided into metabolic diseases affecting the liver (eg. steroid hepatopathy or hepatic lipidosis in diabetic patients), systemic diseases secondarily affecting the liver (eg. reactive hepatitis due to endotoxaemia), and primary hepatitis (eg. acute or chronic hepatitis). Many of the metabolic and systemic diseases in which the liver is not primarily involved do not require specific treatments for the liver (Rothuizen, 2010). In these cases, treatment of the underlying cause, in combination with the regenerative capacity of the liver, will often result in spontaneous recovery of the parenchymal tissue. Diseases of the canine liver parenchyma that require specific treatment include acute hepatitis, chronic hepatitis, copper-associated hepatitis, cirrhosis and hepatic abscessation (Rothuizen, 2010). The World Small Animal Veterinary Association's (WSAVA) Liver Standardisation Group has standardised the histological appearance of common inflammatory liver diseases of dogs and cats.

NON-SPECIFIC REACTIVE HEPATITIS

Non-specific reactive hepatitis represents a non-specific

response to extrahepatic disease, especially febrile illness or inflammation somewhere in the splanchnic bed. Histologically the lesion is characterised by an inflammatory infiltrate in portal areas and in the parenchyma without evident hepatocellular necrosis (van den Ingh, Winkle, Cullen et al, 2006). It results as a consequence of disease occurring outside of the liver, and often does not require specific treatment of the liver (Rothuizen, 2010). Treatment should be targeted on the underlying primary extrahepatic disease.

ACUTE HEPATITIS

WSAVA guidelines characterise acute hepatitis morphologically as a combination of inflammation, hepatocellular apoptosis and necrosis, and, in some instances, regeneration. Acute hepatitis (AH) is seen less frequently than patients with chronic hepatitis (CH). Causes of AH include infectious canine hepatitis (CAV-1), canine herpes virus, drug and toxin induced-hepatitis, leptospirosis, *Clostridium piliformis* (Tyzzer's disease), *Toxoplasma gondii* and septic bacterial diseases (van den Ingh, Winkle, Cullen et al, 2006). Bacterial causes of AH in dogs are uncommon (Rothuizen, 2010), but it is likely that the most common bacterial cause of AH is due to *Leptospira spp* (Bexfield, in press). Drug and toxin ingestion are thought to be the most common cause of AH. Any drug can cause an idiosyncratic reaction. Some drugs, which have been known to cause AH through idiosyncratic reactions include benzodiazepines, trimethoprim-sulphonamide, carprofen and amiodarone. Paracetamol can cause dose-dependant hepatic toxicity (van den Ingh, Winkle, Cullen et al, 2006). However, the majority of cases of acute hepatitis are idiopathic (Bexfield, in press). Clinical signs of AH are usually non-specific, and include waxing and waning gastrointestinal signs, anorexia, weight loss, lethargy, depression and polyuria and polydipsia. Clinical signs of hepatic encephalopathy may also develop. Physical examination findings are generally unremarkable, however, the clinician may be able to palpate an enlarged liver in some animals. Pyrexia or other clinical signs of systemic disease may also be present in animals, that have an infectious aetiology of AH (Bexfield, in press). Clinical pathology is often the first step in diagnostic investigation, and often reveals elevations in ALT, AST, ALP and GGT. It is not possible to differentiate between cases of AH and CH on the basis of these results, however liver function tests are more likely to be normal in dogs with AH (Bexfield, in press). Patients with suspected AH should be tested for leptospirosis, especially if there is concurrent renal involvement. Diagnostic imaging can be performed to investigate cases of suspected AH. Radiography will allow the clinician to assess liver size, however abdominal ultrasonography is the preferred imaging modality and allows assessment of liver shape, size and echogenicity as well as differentiating diffuse and focal hepatic disease (Larson, 2013). Although the above may help guide the clinician, a definitive diagnosis of AH is only possible after histological evaluation of liver tissue. Cytology from

fine needle aspirations of liver tissue is unreliable for the diagnosis of AH and are not recommended. If liver biopsy is not possible due to the patient being systemically unwell, treatment (discussed in the second article of this series) is often initiated based on a tentative diagnosis of AH (Bexfield, in press).

CHRONIC HEPATITIS

CH is the most commonly identified canine inflammatory liver disease (Bexfield, in press). and histological evidence of CH has been found in 12% of dogs undergoing post-mortem examination from primary care practice (Watson, Roulois, Scase et al, 2010). Canine hepatic disease lasting over four to six months in duration is defined as 'chronic' (Willard, 2010). Chronic hepatitis is characterised histologically by a variable mononuclear or mixed inflammatory infiltrate with hepatocellular apoptosis or necrosis, regeneration and fibrosis (van den Ingh, Winkle, Cullen et al, 2006). The development of fibrosis is the key pathological change that leads to the development of CH. Fibrous tissue within the liver alters sinusoidal tone and blood flow and subsequently leads to the development of intrahepatic portal hypertension.¹ The aetiology, if known, should be included as an adjective, eg. 'copper-associated CH' (Willard, 2010), however, in most cases of CH it is not possible to identify the underlying cause of disease and the disease is termed 'idiopathic CH' (Rothuizen, 2010). Several potential causes of CH are known, while others have also been suggested. These include:

- Canine adenovirus-1 (CAV-1) is known to cause acute hepatitis (AH) in non-immune dogs, and CH has also been reproduced in partially immunised dogs challenged with CAV-1;
- Canine acidophil cell hepatitis virus – an infectious agent, potentially a virus, was identified as a cause of AH and CH in 1985 in the UK. Experimentally infected dogs (injected with serum and liver homogenate from infected patients) developed AH, with some progressing to develop CH. However, no specific viral agent was isolated;
- Canine hepatic virus – association with CH is now considered unlikely as recent studies have found no evidence of hepatic virus in large cohorts of dogs diagnosed histologically with CH;
- Leptospirosis – various serovars produce an acute multisystemic disease affecting the kidney, liver and other organs (van den Ingh, Winkle, Cullen et al, 2006). Leptospirosis is an acute disease primarily affecting the kidneys, but can also cause a reactive hepatitis with intrahepatic cholestasis (Rothuizen, 2010). Leptospirosis is known to cause AH, and occasionally CH. Other bacteria are rarely causes of CH;
- Copper – accumulation of abnormal levels of copper has been described in several breeds of dog. Different forms of this condition exist: true 'copper storage disease' as seen in Bedlington terriers. These patients

have an inability to excrete copper into the biliary tract, causing the formation of reactive oxygen species, leading to hepatocyte damage and subsequent CH and cirrhosis. Copper progressively builds up in hepatocytes in zone 3 (centrilobular) over the patient's lifetime. When hepatic tissue is analysed, copper levels >2,000ppm generally indicate that high copper levels are likely to be causing the hepatic disease (Willard, 2010). Another form is 'copper-associated' disease as seen in Skye Terriers, Doberman and West Highland White (WHW) terriers, in which copper accumulates secondary to underlying inflammatory hepatic disease or cholestasis (or increased dietary uptake). In these cases, copper levels do not build up throughout the patient's lifetime, and when liver is analysed copper levels do not correlate with the severity of hepatic disease present (Rothuizen, 2010; Watson, 2004);

- Autoimmunity – although there are some publications, which demonstrate the possible role of various components of the immune system in the aetiology of CH, no studies have yet convincingly demonstrated the presence of a clear underlying autoimmune aetiology to CH;
- Toxin and drug-induced – although acute necrotising hepatitis is more commonly associated with toxin or drug reactions, some can cause chronic disease (eg. phenobarbitone). Some mycotoxins (eg. aflatoxin) may cause acute or chronic liver disease depending on dose and duration of exposure (Watson, 2004).

The liver has a tremendous functional reserve and capacity for regeneration. Overt signs of liver failure do not develop until over 70% of liver functional capacity is lost (Bexfield, in press). Unless another disease or stress causes early decompensation, clinical signs of CH are therefore, often inapparent until the disease is advanced (Willard, 2010). Dogs, which present with 'acute' clinical signs of liver disease, may actually have advanced, near-terminal disease (Willard, 2010). Clinical signs are similar to those described for AH and include vomiting, diarrhoea (which is common), anorexia, weight loss, lethargy, depression and polyuria and polydipsia. Other less common clinical signs include ascites (most often due to portal hypotension, more rarely from

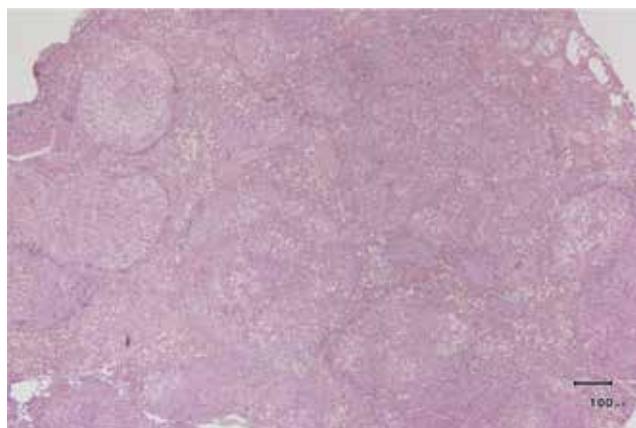


Figure 1: Chronic hepatitis. Definitive diagnosis can only be achieved from histological examination of liver tissue. This dog has bridging fibrosis and regenerative nodules.

severe hypoproteinaemia), and less commonly jaundice, coagulopathies and neurological signs due to hepatic encephalopathy (eg. behavioural changes, seizures, ataxia and head pressing [Willard, 2010]). Animals often have a poor body condition, however physical exam is otherwise often unremarkable (Bexfield, in press).

As with AH, clinical pathology is often the first step in the diagnostic investigation of CH. Although unspecific to CH, 90% of dogs with CH have an elevation in ALT activity, five to 18 times the upper limit of normal (Willard, 2010) and also have elevations of the hepatocellular enzyme AST (Bexfield, in press). Markers of cholestasis (ALP and GGT) are invariably elevated. With progression of disease to hepatic cirrhosis, and due to loss of normal functioning hepatic tissue, hepatic enzymes may fall to within normal reference. Liver enzymes are markers of liver damage, not function. In dogs with CH, liver function becomes progressively compromised due to increasing levels of fibrosis. Some biochemical parameters are very useful indicators of liver function in dogs with CH. Although each parameter is not specific for CH, with progressing disease patients may become hypoalbuminaemic (40% of CH cases, rising to 75% in cirrhotic patients), develop hypocholestraemia, have low BUN levels and may develop prolonged clotting times (PT and APTT). Rarely, patients may become hypoglycaemic.

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Elevations in serum bile acids are usually evident, and occasionally hyperglobulinaemia is found. Haematological changes can include anaemia of chronic disease, microcytosis, leucocytosis and sometimes thrombocytopenia (Willard, 2010). Urinalysis of dogs with CH may demonstrate a low urine specific gravity (<1.030), bilirubinuria, increased urobilinogen, urate crystals or calculi (Bexfield, in press). Diagnostic imaging is often performed to investigate patients with CH, and as with AH ultrasonography is the preferred imaging modality. Ultrasonographic examination, however, is often non-specific, but microhepatica, ascites and nodularity of the liver may be found (Willard, 2010). Radiographs of the abdomen may or may not demonstrate alterations in liver size or the presence of ascites. Definitive diagnosis can only be achieved from histological examination of liver tissue. Again, fine needle aspiration is not reliable for the diagnosis of CH, and is not recommended. After a liver biopsy is performed, all animals should be monitored for signs of bleeding for at least 12

hours post biopsy. The major contraindication to performing a liver biopsy is coagulopathy, and coagulation status (AP, APTT, platelet count and ideally thromboelastography) should be performed prior anaesthetising a patient for liver biopsy. If coagulation times are prolonged, an injection of vitamin K can be given to a patient before re-testing coagulation times again 24 hours later. Fresh, frozen plasma may alternatively be given to assist in the replenishment of deficient coagulation factors (Bexfield, in press).

REFERENCES

Bexfield N. Canine Inflammatory Liver Disease. In *Clinical Small Animal Internal Medicine*. Edited by David Bruyette. John Wiley & Sons, Inc., Hoboken, NJ. In Press

Larson MM. Liver and Spleen. In: Thrall DE (Ed.) *Textbook of Veterinary Diagnostic Radiology*. 6th ed. Missouri: Elsevier 2013; 679-704

Rothuizen J. General Principles in the Treatment of Liver Disease. In: Ettinger, SJ and Feldman, EC (Eds). *Textbook of veterinary internal medicine: diseases of the dog and the cat*, 7th edn, 2 vols. Missouri: Elsevier Saunders 2011; 1629-1637

van den Ingh TSGAM, Winkle TV, Cullen JM et al. Morphological classification of parenchymal disorders of the canine and feline liver 2. Hepatocellular death, hepatitis and cirrhosis. In: *WSAVA Standards for Histological and Clinical Diagnosis of Canine and Feline Liver Diseases*. Elsevier Health, 2006:85-101

Watson P. Chronic hepatitis in dogs: a review of current understanding of the aetiology, progression, and treatment. *The Veterinary Journal* 2004; 167: 228-241

Watson PJ, Roulois AJA, Scase TJ et al. Prevalence of hepatic lesions at post-mortem examination in dogs and association with pancreatitis. *Journal of Small Animal Practice* 2010; 51: 566-572

Willard MD. Inflammatory Canine Hepatic Disease. In: Ettinger, SJ and Feldman, EC (Eds). *Textbook of veterinary internal medicine: diseases of the dog and the cat*, 7th edn, 2 vols. Missouri: Elsevier Saunders 2010; 1637-1642

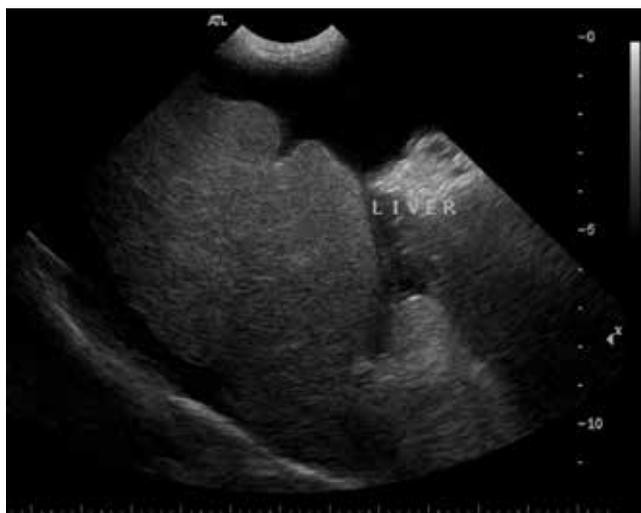


Figure 2: Ascites associated with CH are usually due to portal hypertension, however hypoalbuminaemia may also contribute to its pathogenesis.

READER QUESTIONS AND ANSWERS

- 1: What is the most common form of hepatitis in the dog, acute or chronic?
- 2: **TRUE OR FALSE?** A definitive diagnosis of chronic hepatitis can be made based on clinical signs and blood results alone.
- 3: **TRUE OR FALSE?** Liver biopsy analysis (histopathology) is more reliable than cytology from fine needle aspirate (FNA) samples for the diagnosis of acute and chronic hepatitis
- 4: Before a liver biopsy is taken from a patient with

- suspect CH, what should always first be assessed?
- A Blood pressure
- B Full urinalysis including culture
- C Coagulation status (PT, APTT, thrombocyte count, and ideally thromboelastography)
- D Biochemical profile
- 5: **TRUE OR FALSE?** The liver has tremendous capacity for regeneration. Dogs that present with 'acute' clinical signs of liver disease may actually have advanced liver disease.

ANSWERS: 1: CHRONIC, 2: FALSE, 3: TRUE, 4: C, 5: TRUE