Idiopathic Hepatitis and Cirrhosis in Dogs

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INCIDENCE AND PATHOGENESIS

Primary hepatitis (PH) is the most frequently occurring liver disease in dogs and should be distinguished from nonspecific reactive hepatitis (NSRH). A previous study found that 1% of all referred patients that presented to the author’s university clinic had a form of canine PH. In contrast to human hepatology, the diagnosis of canine hepatitis is based mainly on histologic morphology, and the term, hepatitis, often is used regardless of cause. Regularly encountered forms of PH in dogs include acute hepatitis (AH) and chronic hepatitis (CH) (with or without cirrhosis); less frequently encountered forms are lobular dissecting hepatitis (LDH), granulomatous hepatitis (GH), and eosinophilic hepatitis (EH). For each of these forms, the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group has published standards for diagnosis.1 Of 101 cases of PH referred to the author’s clinic between 2002 and 2006 (Department of Clinical Sciences of Companion Animals, Utrecht University), 21 (21%) had AH (of which CH developed in at least five at a later date), 67 (66%) CH, seven (7%) LDH, one (1%) GH, and one (1%) EH. Of the CH cases, after re-evaluation of the biopsies with copper staining, 36% seemed copper associated (CH[ca]), higher than expected, and 64% of the CH cases had an unknown cause and were considered idiopathic (CH[i]). Among dogs with CH(i) and CH(ca), approximately 50% had cirrhosis at initial diagnosis, and both groups contained several female Labrador retriever dogs (seven and five, respectively).

In different publications and case reports, a wide variety of causes for hepatopathy in general has been documented, including microorganisms, toxins and drugs, immune-mediated reactions, and breed-associated metabolic errors.2 The inherited disorders of copper metabolism, in particular, have received much attention in the last few decades.3–9 In spite of a large effort, however, the majority of PH cases remain of idiopathic origin. Although hepatitis in dogs has been characterized extensively, there are no data published on the occurrence of the various WSAVA-classified forms of hepatitis in a clinical population, progression between those forms, or occurrence of idiopathic and copper-associated forms of hepatitis.10–12

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ACUTE HEPATITIS

In the field, most cases of AH probably are missed. Dogs with AH are ill for a couple days, after which they recover spontaneously with or without supportive care without knowing what has happened. The most aggressive form of AH, fulminant hepatitis, is rapidly progressive within hours or days. In the author’s referral clinic, these patients are not often seen (alive), probably because the time to get to the clinic via the referring veterinarian is too long. Canine adenovirus-1 (CAV1) is a known cause for the development of AH (sometimes fulminant). Because of vaccination, AH caused by CAV1 has been controlled effectively and practically eliminated from the domestic dog population.

There is an impression that, although initially diagnosed as acute, some cases remain acute for months on histopathology and might be considered more or less CH, although fibrosis is lacking. This form of hepatitis, although not a WSAVA-classified form, might be considered subacute hepatitis. When starting with prednisone treatment of subacute hepatitis in the clinically chronic stage, this hepatitis does not seem to respond clinically or histopathologically.

Twenty-five percent of the dogs with AH had AH(ca). Hepatitis resulting from primary copper accumulation starts somewhere in the process of developing hepatitis and, depending on the stage at which the diagnosis is made, can be acute or chronic. This finding suggests that even when dealing with a dog that has hepatitis with a history of sudden onset, suggesting an acute inflammation, copper may be the cause, and it is advisable to ask for a routine copper staining in this type of patient. From 21 dogs with AH initially diagnosed, at least five had CH when a second liver biopsy was taken 6 weeks later.

CHRONIC HEPATITIS AND CIRRHOSIS

CH is a frequently occurring disease in dogs. Approximately two thirds of the patients with PH referred to the author’s university clinic had CH at initial diagnosis, and several more patients with AH progressed histologically to CH. In humans, the diagnosis of CH is based on patient history and results of histopathologic examination of liver biopsies. Because the diagnosis is etiology-based, a specific etiology-focused treatment approach is possible. In contrast, diagnosis in dogs is mainly morphology based with severity based on the type and distribution of inflammatory cells, hepatocellular apoptosis and necrosis, and the abundance and localization of fibrosis. In most cases, there is no evidence of a cause, resulting in a large proportion of CH(i) cases. This poor understanding of the cause of CH(i) results in limited options for adequate treatment and in variable results. Although probably not the initial cause, oxidative stress plays an important role in the maintenance and progression of disease, and, for this reason, antioxidants might play a beneficial role in the treatment of CH, at least. For decades, canine CH(i) patients have been treated mainly with orally administered immunosuppressive medication, of which prednisone is most commonly used. The efficacy of prednisone has been described in one publication. In this retrospective study, a prolonged survival time was demonstrated for prednisone-treated canine CH patients in comparison with untreated patients. These results indicate a positive long-term effect of prednisone in the treatment of CH(i). In addition to anti-inflammatory effects, corticosteroids have (weak) antifibrotic properties. A retrospective histopathologic evaluation of inflammatory activity and fibrosis formation in dogs with CH(i) before and after a 6-week treatment with prednisone, although not double-blind or placebo controlled, found a reduced inflammatory activity and a stable fibrotic...
situation, the latter suggesting a fibrosis inhibitory effect of prednisone (Poldervaart, in preparation).

CIRRHOSIS

Fibrosis, a hallmark of CH, is defined as a detectable deposit of extracellular matrix (ECM). Cirrhosis is the end stage of CH and is defined as a diffuse process characterized by fibrosis of the liver and the conversion of normal liver architecture into structurally abnormal nodules, micro- or macronodular.\(^1\) Cirrhosis is the result of an accumulation of ECM materials, which is the resultant of increased synthesis or decreased breakdown. The bulk of ECM in the fibrotic liver is produced by myofibroblast (MF)-like cells. Three different MF-like cells are described based on location and immunohistochemical profile.\(^13\) These comprise portal or septal MF; interface MF; and perisinusoidally located hepatic stellate cells, which are nonparenchymal, quiescent cells that are activated by hepatic injury and produce most of the factors that lead to hepatic fibrosis. One of the most important of these factors is transforming growth factor-beta (TGF-\(\beta\)), which acts via its two receptors, TGF-\(\beta\) receptor type I (TGF-\(\beta\) RI) and TGF-\(\beta\) receptor type II (TGF-\(\beta\) RII), at the cell surface and the intracellular substrates, the Smad proteins. TGF-\(\beta\) stimulates fibrosis by inducing the up-regulation and the release of many of the ECM components (collagens and glycoaminoglycans) and inhibitors of the metalloproteinases, preventing the breakdown of the ECM.

Important regulators of ECM turnover and breakdown are plasminogen activator–plasmin system components. Urokinase-type plasminogen activator (uPA) generates plasmin from circulating plasminogen by proteolytic cleavage. This plasmin is capable of degrading ECM components directly by proteolysis and indirectly by inhibiting deposition of ECM by activation of matrix metalloproteinases. In this way, an up-regulation of uPA in the liver might inhibit the deposition of ECM and reverse hepatic fibrosis. Overall, matrix remodelling is an important component of liver regeneration.

Cirrhosis is considered irreversible, although the point at which this happens is not well defined. Until now, no antifibrotic therapy has been clinically available, and in humans, liver transplantation remains the only treatment option in cases of hepatic dysfunction resulting from cirrhosis. Recent evidence suggests that the process of fibrogenesis might be reversible,\(^14,15\) opening possibilities for evaluation of newly designed antifibrotic therapies.

LOBULAR DISSECTING HEPATITIS

The clinical symptoms in dogs with LDH are more or less acute, but on histopathology, they are diagnosed as having a CH with cirrhosis based on a massive deposition of fibrous tissue around individual or small groups of hepatocytes. The cause of this form of hepatitis is unknown. In most cases, patients with LDH are young animals (average age 2.3 years in the author’s clinic) and die shortly after diagnosis, with an estimated median survival time of 0.7 ± 0.01 months (\(n = 7\), 2002–2006) despite treatment consisting mostly of prednisone and sometimes diuretics because of the development of severe ascites resulting from portal hypertension.

NONSPECIFIC REACTIVE HEPATITIS

Nonspecific reactive hepatitis (NSRH) is an aspecific response to extrahepatic disease processes, especially inflammation somewhere in the splanchnic bed (gastrointestinal tract or pancreas) or a systemic illness with fever. It also can be found as a residual lesion of a previous inflammatory primary intrahepatic disease. NSRH, a secondary
problem, does not have to be treated. It is essential to look for the primary cause (gastrointestinal tract or systemic illnesses) and to treat that underlying cause.

CLINICAL PRESENTATION

Patients with PH seen in the author’s clinic present, in most cases, with nonspecific clinical signs. The most noticed symptoms mentioned by owners are decreased appetite (50%), vomiting (48%), polyuria-polydipsia (47%), reduced activity (39%), weight loss (28%), jaundice (24%), diarrhea (23%), and abdominal distension (21%). Episodic neurologic symptoms resulting from hepatic encephalopathy rarely are mentioned. Acholic feces, a specific indicator for extrahepatic biliary obstruction, are not seen in cases of PH. Depending on the form of hepatitis, signs can be obvious from hours (acute fulminant hepatitis) to months (CH).

DIAGNOSTIC EVALUATION

Physical Examination

At general appearance, dogs with CH, but not AH, have a slight to moderate muscle atrophy. Dogs with ascites resulting from portal hypertension show abdominal distension.

Physical examination related to liver diseases concentrates on the mucous membranes and abdominal palpation. In cases of hepatomegaly, examination of the circulation is indicated to detect or exclude cardiac disease. The mucous membranes are normal in most patients with liver disease. Abnormalities may include icterus, pallor, and indications for coagulopathy. Very pale mucous membranes in the presence of icterus indicate that the liver dysfunction is secondary to hemolytic anemia, and a further workup should focus on this problem. Petechiae, an indicator for thrombocytopenia or thrombocytopenia, although rarely seen in patients with PH, can be found as a result of disseminated intravascular coagulopathy.

Hepatomegaly, as a finding at abdominal palpation, is rare in dogs with PH. Ascites, leading to abdominal distension, resulting from portal hypertension or hypoproteinemia, also may be an indication for liver disease, but there are many diseases of origins other than hepatic that may induce ascites formation. Abdominal palpation also may reveal splenomegaly in cases of portal hypertension.

In most dogs with hepatitis, physical examination reveals no specific information. Therefore, in the majority of cases that involve symptoms (described previously), laboratory investigation is required to detect or exclude a liver disease.

Blood

Blood work can be used for two purposes: first, to detect or to exclude a (primary) liver problem, and second, to screen for the overall status of a patient. To address the first, blood work should consist of, at minimum, serum bile acids, alkaline phosphatase (AP), and alanine aminotransferase (ALT). In almost all cases of PH, one of these parameters is out of the upper reference range. Liver enzymes are indicators for cellular damage, whereas bile acids are a functional parameter. Of the liver enzymes, ALT is the first to increase when PH is present. Adding more (liver) enzymes to the diagnostic panel does not give more information. When patients with jaundice present to a clinic, this part of the blood workup is not necessary. For the second purpose, a complete blood cell count and a biochemistry and coagulation profile are necessary. The biochemistry profile should include at minimum—in addition to serum bile acids, AP, and ALT—urea, creatinine, total protein, albumin, sodium, and potassium. If further workup liver biopsies are needed, a coagulation profile has to be determined.
This test should be performed shortly before the biopsy procedure because coagulation parameters may change quickly in patients with hepatitis (inadequate vitamin K absorption, reduced production of coagulation factors, or increased consumption [disseminated intravascular coagulopathy]). In the author’s clinic, prothrombin time, activated thromboplastin time, fibrinogen concentration, and platelet count are measured. Fibrinogen concentration, in particular, is a critical indicator, and a concentration less than 1 g/L is a contraindication for taking a liver biopsy, which happens in approximately 8% of cases of PH. This lowered fibrinogen concentration increases in more than 90% of these cases above the critical level after a 1-week treatment with prednisone/prednisolone so that a liver biopsy can be taken safely at that time.

There is some debate on what type of liver function tests to use for a functional evaluation. Worldwide, the serum bile acid tolerance test (comparison of pre- and postprandial serum bile acids) commonly is used. A major reason for this is that it is easily accessible for private clinics because samples can be sent to laboratories for measurement. The serum bile acid tolerance test does not give much additional information regarding the liver function above only preprandial serum bile acid concentration; for screening for portosystemic shunting, determination of the basal plasma NH₃ concentration is a better test.¹⁶ When the basal plasma NH₃ measurement is not informative, the rectally applied NH₃ tolerance test confirms or excludes the presence of portosystemic shunting. Measurement of plasma NH₃, which should be done immediately after sampling, can be more problematic in private clinics, although in recent years equipment for ammonia measurement has become more accessible for private clinics.

**Ultrasound scan**

For further diagnostic workup, ultrasound scan is needed. With ultrasonography, the liver parenchyma, gallbladder/biliary tree, portal vein, acquired shunting (when present), and ascites can be evaluated. In a recently performed evaluation of patients with PH, in 20% of the cases no abnormalities were found at abdominal ultrasonography. In approximately 25% of the cases, the liver was enlarged, irrespective of type of hepatitis. Ascites, in cases of liver disease, resulting from portal hypertension, often combined with a slightly to moderately decreased plasma albumin concentration, was found mainly in dogs with CH and LDH. In cases of ascites resulting from liver failure, there also is a high chance of finding acquired portosystemic collaterals. The best place to look is the region caudal to the left kidney. The finding of enlarged portal lymph nodes, ascites, or a decreased liver size has a negative prognostic value.

Finally, ultrasonography is necessary for guiding liver biopsies with Tru-Cut needles (Manan Medical Products, PBN Medicals, Stenlose, Denmark).

**CT/MRI**

For a further workup of patients with hepatitis, CT or MRI normally is not necessary. In cases in which a primary liver tumor is suspected, based on ultrasonography, and surgical intervention is needed, preoperative screening with CT or MRI with contrast is helpful in estimating size and localization of the tumor and visualizing the presence of tumor metastasis.

**Liver Biopsy: Pathology**

A liver biopsy is considered the gold standard for establishing a diagnosis of PH and to differentiate, when necessary, PH from NRSH. Fine-needle aspiration is not sufficient for diagnosing any form of hepatitis (primary or secondary). Liver biopsies can be ultrasound guided with a True-Cut needle or blind by aspiration using a syringe attached to
the needle (Menghini technique). At least two or more samples are advisable to minimize sampling errors. Because approximately one third of the cases of PH referred to the author’s clinic are copper associated, the author advocates routine staining for copper (eg, with rubeanic acid) in addition to hematoxylin-eosin staining as standard procedure for liver histology in dogs.

**TREATMENT AND PROGNOSIS**

Most cases of idiopathic AH do not need treatment, but, depending on the severity of vomiting and presence of dehydration, antiemetic treatment and fluid therapy are indicated. Most dogs with AH recover after several days without medical interference. Progression from (initial) AH to its chronic counterpart may occur, resulting in recurrence of clinical signs. It is advisable to repeat the liver biopsy 6 to 8 weeks after the initial diagnosis to control if the hepatitis has been solved or has progressed to CH. CH(i) is treated as an immune-mediated disease with oral submission of prednisone or prednisolone combined with supportive therapy (eg, antiemetic, antidiuretic, fluid therapy, and dietary adjustments). As discussed previously, only one publication (a retrospective evaluation) is available on the efficacy of prednisone in the treatment of CH in dogs, which showed a prolonged survival time for dogs with CH when treated with prednisone (0.6–1.1 mg/kg per day).10 The response to prednisone therapy is controlled on a regular basis by liver biopsy, usually at a 6-week interval, and therapy is continued until histologically no hepatocellular death and inflammation are observed. In humans, the application of glucocorticoid treatment is indicated in alcohol-induced cirrhosis and autoimmune hepatitis in contrast to virally induced hepatitis, where it is contraindicated. Histologic similarities between human virally induced hepatitis and canine CH could indicate a reverse effect of prednisone efficacy. The majority of dogs with CH(i) referred to the author’s clinic (2002–2006, n = 36) treated with prednisone (1 mg/kg per day), initially aimed at a 6-week treatment period, showed an estimated median survival time of 9.9 months. When only the CH(i) with cirrhosis cases treated with prednisone (n = 19) were included, the median survival time was 1.3 months, stressing that the presence of cirrhosis is a strong negative prognostic indicator. In the past, when unacceptable side effects (extreme polyuria-polydipsia, severely increased appetite, and reduced exercise tolerance) resulting from prednisone/prednisolone medication occurred, the author and colleagues tapered the dosage of prednisone/prednisolone and started a combined therapy with azathioprine (1 mg/kg per day) for 6 weeks. Because of increased awareness of toxic side effects of cytostatic drugs in households (young children and pregnant women), however, and because treatment of CH(i) has no proved benefit, the author does not advocate this combination therapy any longer.

Other than immunosuppressive medication, proposed medicinal options for treatment of CH(i), based mainly on extrapolated human data and personal experiences, are ursodeoxycholic acid (UDCA) (7.5 mg/kg twice a day); antioxidants, such as S-adenosyl-L-methionine (SAMe) (10 mg/kg twice a day); silymarin (100–200 mg/dog single oral administration); vitamin E (100–400 IU/day); and the antifibrotic drug, colchicine (0.025 mg/kg/day). UDCA is a synthetic nontoxic hydrophilic bile acid that provides a few positive actions. First, UDCA enhances the bile flow, and in this way it stimulates the excretion of inflammatory products. Second, UDCA decreases by dilution the concentration of the endogenous, more toxic bile acids. Third, it modulates the immune system, resulting in a reduction of the immune response, and fourth, there is proof that UDCA has antioxidative properties. The author’s clinic recently started a trial with UDCA to evaluate if this drug might be a fair alternative for
prednisone as a treatment of CH(i). SAMe is a natural metabolite in hepatocytes and is a precursor of glutathione. It is important in the defense against oxidative stress, and exhaustion might occur as a result of exposure to toxic substances in patients with CH. Silymarin seems to act as a strong free-radical scavenger by increasing cellular levels of superoxidisedismutase, important in enzymatic defenses against oxidative stress—it regulates cell membrane permeability and has been shown to inhibit leukotriene synthesis and the effects of tumor necrosis factor alpha. Evidence from many human and veterinary reports underlines the protective effects of silymarin in patients with mushroom or acetaminophen intoxications.\(^{18,19}\) Vitamin E is a nutritional antioxidant that protects against different routes of membrane peroxidation.

Colchicine has been proposed for treating CH fibrosis presumably by decreasing the formation and increasing the breakdown of collagen, but benefit is unproved, and there is little experience with colchicine in dogs. It can be a toxic drug after small overdoses. It is not advisable to use this drug in dogs until it is proved effective.

Many of the medications discussed previously generally are accepted and clinically used for the treatment of liver diseases, mostly as part of a multidrug therapy. Unfortunately, until now, for most of these drugs, critical scientific evaluation of their effectiveness is lacking.

If there is clinical evidence of portal hypertension (ascites or hepatic encephalopathy), treatment with spironolactone, a potassium-sparing diuretic (1–2 mg/kg twice a day), lactulose (0.5 mL/kg 2 to 3 times a day), and dietary adjustments (high-quality protein diets, moderately restricted) can be started. Spironolactone is preferred to furosemide because of the underlying pathophysiology of portal hypertension in which the rennin-angiotensin-aldosterone system is activated. In cases of severe ascites, a combination of spironolactone and furosemide may be effective. Lactulose, a synthetic disaccharide fermented by colonic bacteria into short-chain fatty acids, helps acidify the colonic environment to trap NH\(_3\) (NH\(_4^+\)) so that it remains mainly in the feces and does not enter the portal circulation, reducing clinical signs of HE. When the portosystemic collaterals are optimally activated, and plasma albumin concentration is above the edema border (>15 g/L), ascites can disappear, and diuretic treatment might be stopped. This activation of collaterals normally takes 2 to 3 weeks. Symptomatic treatment of gastric erosions and ulceration consists of sucralfate (1 g by mouth 3 times a day) and a H\(_2\)-blocker (ranitidine [1 mg/kg twice a day], famotidine, or omeprazole [1 mg/kg once daily] [avoid cimetidine]).

In cases of CH(ca) or AH(ca), an etiology-based specific therapeutic approach is applied by feeding a low-copper diet, submission of a copper chelator (eg, D-penicillamine, 10–15 mg/kg twice a day), or submission of exogenous zinc (10 mg elemental zinc/kg twice a day). Penicillamine has, in addition to metal chelating properties, an immunomodulatory effect and possesses antifibrotic activity via inhibition of collagen crosslinking, causing collagen to be more susceptible to degradation.

**SUMMARY**

Poor understanding of the causes of PH, especially CH(i), results in limited options for adequate treatment and variable results. Elucidating the causes, aside from the copper-associated form of hepatitis, is of utmost importance to find etiology-based treatments for canine (chronic) hepatitis, when possible, most likely resulting in a better prognosis. The prognosis for patients with CH(i), with developed cirrhosis, is poor. Because many AH and CH cases are concluded to be copper associated (25%–30%), it is advisable to ask for a copper staining (eg, rubeanic acid) in addition to routine hematoxylin-eosin staining when sending liver materials to a pathology
department; otherwise, this diagnosis can be missed and patients do not get appropriate treatment with copper-binding agents.

REFERENCES