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HEPATITIS IN DOGS: NEW CONCEPTS IN PATHOGENESIS AND TREATMENT

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The diagnosis of hepatitis (acute, chronic, etc.) is only possible with histology of the liver. The histopathologic diagnosis should include the type, pattern and extent of the necrosis and inflammation, and the possible cause, and in more chronic cases the presence, pattern and extent of fibrosis and regeneration. The activity of the inflammation is defined by the amount of hepatocellular necrosis and inflammation, and the chronicity is determined by the amount of fibrosis.

Acute hepatitis

Etiology

Acute hepatitis can be caused by chemicals (the most familiar are organic solvents such as CCl4, and phosphorous), drugs (including the antibiotic nalidixine acid), viral infection (infectious canine hepatitis), and mycotoxins (especially aflatoxin B1). Hepatitis resulting from sepsis (reactive hepatitis), leptospirosis, and haemolysis are discussed in other sections.

Pathogenesis

In an acute hepatitis all of the enzymes are usually definitely elevated. Fever can, but does not always, occur as a result of pyrogens from necrotic tissue and from reduced removal of endotoxins and bacteria from the portal blood. DIC often occurs. Very extensive liver cell necrosis is called fulminant hepatitis. It leads to the development of hepatic encephalopathy, DIC, jaundice, and hypoglycaemia. This severe form progresses rapidly to coma and death. Acute hepatitis is characterized by liver necrosis and the accompanying inflammation. The necrosis is usually a liquefying necrosis with collapse of the reticular framework. The inflammatory infiltrate consists of round cells and neutrophils. There are also ceroid-filled macrophages called “scavenger cells”. Infection with canine adenovirus-1 is usually characterized by confluent and bridging necrosis in the centrilobular zone and by the presence of intranuclear inclusions in hepatocytes and Kupffer cells. The virus can also be demonstrated in a histologic section of liver by immunofluorescence. Acute hepatitis may also be caused...
by various toxins, such as mushroom toxins (Amanitum), blue-green algae toxins (Cyanophyceae) or dose-dependent drug toxicity (acetaminophen in dogs and cats).

**Symptoms**

Acute illness, apathy, sometimes fever, anorexia, vomiting, dehydration, sometimes icterus, in very severe cases DIC and tendency for bleeding. The clinical picture is entirely dependent upon the severity of the liver damage and may vary from insignificant to fulminant lethal disease. Acute hepatitis is usually a moderately severe disease which may recover completely.

**Diagnosis**

Blood examination: elevation of liver enzymes, especially ALT. The diagnosis is confirmed by liver biopsy (coagulation should be checked first, since it is often abnormal). Hepatic encephalopathy in fulminant hepatitis is characterized by high blood NH3 values. Often there is no identifiable cause.

**Management**

Usually only symptomatic treatment is possible: iv fluid to correct hypovolemia, shock, acidosis or alkalosis, hypoglycaemia, and electrolyte disturbances. Avoid corticosteroids; in acute infections they are definitely contraindicated. The prognosis is entirely dependent on the degree and amount of liver damage. Phalloidine and acetaminophen intoxication cause oxidative damage and should be treated with silymarin (50 mg/kg/day) for 3-5 days. Silymarin has been reported to lose its effect when given a few hours after intoxication. Acetaminophen intoxication may also be treated with the combination of N-acetylcysteine (140 mg/kg PO, every six hours during three days), vitamin C (25-35 mg/kg PO, every six hours for two days), and cimetidine 5 mg/kg/bid for 4 days. Dogs with acetaminophen intoxication may have hemolysis and blood transfusion may be required.

**Follow up**

Acute hepatitis recovers spontaneously in most cases, but about 30% progresses to a chronic hepatitis. The chronic disease usually does not give clinical signs in the first months, so that the dog seems to have recovered completely. Chronic liver damage will cause clinical signs only later on, and in that stage it is harder to achieve complete recovery than in the early phase. It is therefore recommended to perform a control liver biopsy four to six weeks after the diagnosis of acute hepatitis.

**Chronic hepatitis and Cirrhosis in the dog**

These two subjects are discussed together because they have the same pathogenesis and the clinical and pathological changes often overlap. Chronic hepatitis is characterized by periportal fibrosis, infiltration of lymphocytes and plasma cells, and periportal liver cell apoptosis or necrosis. Apoptotic liver cells become smaller and acidiphilic; they are known as acidophilic bodies. The limiting plate, which is the layer of cells dividing the portal tracts from the liver parenchyma, may become disrupted with expansion of the inflammatory reaction from portal areas into the parenchyma. This invasion may extend to form porto-portal or porto-central bridging fibrosis. If fibrosis forms septa connecting portal and centrolobular areas, the normal functional architecture of the liver lobules becomes permanently disturbed: this is called cirrhosis. The fibrosis, especially in cases of cirrhosis, obstructs the normal blood flow to the liver, which primarily affects the low pressure portal
blood supply. Portal blood is required to activate local growth factors in the liver, so that decreased portal perfusion also contributes to decreased liver regeneration. All together, advanced fibrosis extends to cirrhosis in a negative vicious circle. Chronic hepatitis and cirrhosis are associated with variable degrees of intrahepatic cholestasis, but in most cases there is no clinically visible icterus.

**Etiology**

Chronic hepatitis may be the result of a viral infection. The common canine adenovirus-1 (CAV1) of infectious canine hepatitis is the only known canine hepatitis virus. CAV1 virus infection in non-vaccinated animals gives fulminant hepatitis. It is likely that there are more hepatitis viruses to cause chronic hepatitis. The lymphocytic and plasmacellular inflammation, and the good response to immune suppressive drugs indicate that a self-per-petuing autoimmune type of liver cell necrosis causes the chronic progression. Chronic hepatitis and cirrhosis may also result from chronic lesions caused by chemicals or toxins (aflatoxin). Metabolic errors in the liver, primarily inherited copper toxicosis also leads to damage of hepatocytes with secondary hepatitis and fibrosis; this reaction, however, begin zones 3 of the acini instead of in the portal areas.

**Pathogenesis**

Chronic hepatitis may be a chronic extension of acute hepatitis, but in most cases the first presentation of signs is in the chronic stage. The gradually progressive liver cell necrosis may cause a continuing elevation of all liver enzymes and the bile acids. Liver function is diminished by the loss of functional tissue and reduced portal blood flow. There are often low albumin and fibrinogen levels. The conversion of ammonia remains adequate until portosystemic collaterals develop. Hepatic encephalopathy may develop if portosystemic collaterals are formed. Hypoalbuminemia and portal hypertension may cause ascites (transsudate). In the breeds in which an abnormal copper metabolism causes hepatitis, the gradual accumulation of copper usually leads to clinical signs at an age of 4-6 years. The most frequently affected breeds are Labrador retrievers (golden retrievers to a lesser extent), Dobermann Pinschers, all spaniel breeds, Bedlington terriers, and west Highland white terriers. The incidence of chronic hepatitis is relatively high; it is one of the most common liver diseases in companion animals and accounts for about 1% of the cases in a referral clinic.

**Symptoms**

The most frequent symptoms are apathy, reduced appetite, vomiting, poor endurance, polydipsia, and sometimes icterus. Only in advanced cases there may be ascites and hepatic encephalopathy. Diarrhea is not a usual sign of hepatitis.

**Diagnosis**

The diagnosis can only be made by liver biopsy. Misdiagnosis is avoided by taking two to three biopsies. Ultrasonography prior to biopsy is advised; cirrhosis may be suspected by the appearance of a small liver with an irregular surface and structure. Many cases of (acute or) chronic hepatitis show no abnormalities at all with ultrasonography.

**Management**

Prednisolone in a dose of 1 mg/kg/day is required for a long time, preceded by a dose of 2 mg/kg/day for one week. Medication must be continued until there is no doubt about the complete histological recovery. If therapy is stopped too
soon the hepatitis will recur. Without treatment, the disease progresses to cirrhosis. Apart of specific treatment directed at the hepatitis, advanced stage cases need supportive care directed at dehydration and management of the risks of HE. There is only risk for HE when the outcome of an ammonia tolerance test is abnormal.

The prognosis of chronic hepatitis is usually good; the disease can be cured completely in most dogs. Sometimes there are recurrences and than the treatment is repeated. Depending on the presence of collaterals dog may require permanent support with a liver support diet and lactulose. Remission of the lesions of cirrhosis is impossible, but such dogs can often be maintained at a fairly satisfactory level for a long period.

**Hepatitis caused by copper accumulation**

**Etiology**

Hepatitis in copper storage diseases occurs as a result of an inherited defect in the copper metabolism of hepatocytes, resulting in impaired excretion into the bile. Food contains an excess of copper, which is absorbed in the small intestines and cleared from the portal blood by the liver. The excess is normally excreted into the bile by the hepatocytes and so cleared from the body. In inherited copper storage diseases the gradually accumulating copper in hepatocytes causes oxidative damage and finally liver cell necrosis followed by an inflammatory reaction. Accumulation of copper and inflammation occur around the central veins, whereas other forms of chronic hepatitis concentrate in and around the portal areas. The gradual accumulation leads to clinical disease usually at an age of 4-7 years. This disease occurs in different breeds: Bedlington terriers, Labrador, Dobermann Pinschers, all spaniel breeds, west Highland white terriers, Dalmatian dogs, and Skye terriers. For Bedlington terriers ther is a DNA test which also diagnoses symptom-free carriership.

**Pathogenesis**

The increased copper concentration in the liver can be confirmed after 1 year of age; before that age some dogs with the disease have not yet stored sufficient copper to distinguish them from normal animals. Oxidative damage to cell organelles causes cell death followed by an inflammatory reaction when. A chronic persistent hepatitis develops and the general reaction of the liver is loss of regenerative capacity and formation of fibrous tissue. In the end stage, cirrhosis may develop. The normal concentration of copper in the canine liver is between 50 and 400 μg/g dried tissue. In Dobermanns the disease affects only females, typically at an age of 4-7 years. In Labradors there is also a femal over representation.

**Symptoms**

The symptoms are the same as seen in other forms of chronic hepatitis: apathy, reduced appetite, vomiting, poor endurance, polydipsia, and sometimes icterus

**Diagnosis**

The diagnosis hepatitis is based on histological examination of liver biopsies; the association with copper is based on histochemical staining (eg, with rubeanic acid) to make copper visible. The DNA test in Bedlingtons can be performed in any tissue.

**Management**

Copper storage disease should be treated with a copper binding chelating drug. Penicillamine is the most
widely available drug, which is given in two daily doses just before a meal in a total daily dose of 25 mg/kg. Penicillamin binds the copper coming in the circulation after eating and the bound complex is excreted in the urine. Gradual removal of free excessive copper reduces the activity of the hepatitis. The minimum period for treatment before evaluating the liver with a biopsy is six months. Female Dobermanns with this disease used to die with usual medications, but ever since we treat them with penicillamine, recovery is the rule. Like other forms of hepatitis, the response to treatment should be evaluated by repeated liver biopsies; for most copper storage diseases an interval of three months is appropriate. If the hepatitis is cured, recurrence should be prevented because the genetic basis for abnormal copper metabolism is of course remaining. Long term prevention may be achieved with zinc, which may be given as zinc gluconate in a dosage of 30 mg/kg/day in divided doses with each meal. Zinc induces the production of metallothionein in the intestinal mucosa, which binds copper, thus preventing its absorption. Zinc gluconate has virtually no side effects (sometimes transient nausea), and is very cheap. Another measure to prevent further accumulation is to give a low copper diet. The commercial liver support diets contain much lower amounts of copper than any other commercial or home made diet, and are recommended.

Lobular dissecting hepatitis

Etiology

The etiology of this disease is unknown. The author has seen this form of hepatitis in kennels where one dog after another got ill, at different ages. In the absence of indications for toxic causes this was suggestive for an unknown infectious origin.

Pathogenesis

This is a diffuse fibrosis with pericellular fibrosis around all hepatocytes. The amount of fibrous tissue is excessive and therefore there is usually severe portal hypertension, which may quickly cause ascites, portosystemic acquired collaterals and hepatic encephalopathy. The progression is usually much more rapid than the regular form of chronic hepatitis; the course of this disease takes weeks rather than months. The clinical picture closely resembles that of cirrhosis and congenital portal vein hypoplasia. In fact, the correct term for this disease rather is cirrhosis (deranged liver lobe architecture) than hepatitis. The liver is too small and has a smooth or finely granular surface.

Symptoms

Weight loss, vomiting, polyuria, followed by ascites and hepatic encephalopathy,

Diagnosis

Abdominal fluid is clear, colourless or yellow in case of icterus. At blood examination liver enzymes may or may not be increased, but bile acids are. Ammonia may be elevated and the ammonia tolerance test is abnormal.

Liver biopsy is diagnostic and reveals the characteristic histologic changes. Percutaneous liver biopsy with the Menghini technique is usually difficult (small, firm liver that, floating away in the ascites), so that ultrasound guided biopsy with a biopsy gun may be necessary.

Management

Treatment as for chronic hepatitis, however, the prognosis is much poorer for this specific form of hepatitis.