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CHRONIC LIVER DISEASES IN DOGS

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Introduction

Chronic liver disease in dogs has multiple origins: circulatory, inflammatory and cirrhotic, infectious, hepatic reversible and metabolic, neoplastic and bile duct disease (table 1) (1,2). Clinical presentation varies widely according to disease stage: absent, general, gastrointestinal, nervous and urinary signs. Diagnostic work-up includes several stages: hepatocellular lesion and function tests, diagnostic imaging and, often necessary for definitive diagnosis, hepatic biopsy and histopathologic examination. Once an accurate diagnosis established, optimal treatment strategies can be chosen.

Table 1: WSAVA classification of chronic liver disease in dogs

- Circulatory disorders of the liver
  - Congenital portosystemic shunts
  - Heart, caudal vena cava or hepatic vein outflow disturbances
  - Disorders associated with portal hypertension
    - Portal vein obstruction, primary portal vein hypoplasia, intra-hepatic arterio-venous fistula, others
- Chronic hepatitis and cirrhosis
  - Chronic hepatitis
  - Copper-associated hepatitis
  - Lobular dissecting hepatitis
  - Non-specific reactive hepatitis
  - Eosinophilic hepatitis
  - Cirrhosis
- Reversible hepatocyte injury
  - Steroid-induced hepatopathy, hepatic amyloidosis, others
- Toxic liver injury
- Hepatic abcesses and granulomas
- Hepatic metabolic storage disorders
- Hepatic neoplasia and hyperplasia
  - Nodular hyperplasia, regenerative nodules
  - Hepatocellular: nodular adenoma, carcinoma
  - Cholangiocellular: adenoma, carcinoma
  - Others
- Biliary disorders
  - Biliary cystic disease and biliary atresia
    - Solitary cysts
    - Congenital cystic liver disease
    - Biliary atresia
  - Cholestasis
  - Cholangitis
    - Neutrophilic
    - Lymphocytic
    - Destructive
    - Associated with liver fluke infestation
  - Gallbladder diseases
    - Cholelithiasis
    - Cystic mucinous hyperplasia
    - Gallbladder mucocele
    - Cholecystitis
    - Infarction of the gallbladder

Breed, age and sex predisposition

Hereditary copper-associated hepatitis has been described in various breeds (Bedlington terrier, West Highland white terrier, Skye terrier, Doberman pinscher, Dalmatian and Labrador) and suspected in others (3-9). Chronic hepatitis is commonly seen in young adults with progression toward cirrhosis possible at any age (3). Young American and English cocker spaniels are at risk of chronic hepatitis with rapid progression to

cirrhosis, males are overrepresented. Female dogs seem predisposed for chronic idiopathic and copper-associated hepatitis (10). Chinese Shar Pei dogs are predisposed for hepatic amyloidosis. (3). Congenital vascular disorders are rather observed in young purebreed dogs, particularly Yorkshire, Maltese and Cairn terriers, miniature schnauzer and Irish wolfhound amongst others.

Clinical signs

The liver plays a central role in numerous processes including carbohydrate, lipid and protein metabolism, metabolite and xenobiotic detoxification, vitamin, metal (trace), fat and glycogen storage, fat digestion and immunoregulation (3). Clinical signs of chronic hepatic disease (table 2) reflect deficiencies in these functions and vary with disease stage. The liver has enormous reserve capacities, explaining why some more specific signs of hepatic disease as icterus, hypoglycemia, coagulation abnormalities, hepatic encephalopathy or ascites occur late in the disease progress. Early clinical signs are often non specific: lethargy, anorexia, vomiting, PUPD, etc.

Table 2: Clinical signs encountered in chronic liver disease

General clinical signs	Gastrointestinal signs	Neurologic signs	Urinary signs
Anorexia Lethargy Weakness Weight loss Abdominal distension Icterus Abdominal pain Hepatomegaly Pale mucous membranes Fever	Vomiting Diarrhea Melena Hematemesis Acholic feces	Behavioral changes Ptyalism (cat) Mental state changes (disorientation, stupor, coma) Irritability, aggressiveness Seizures	PUPD Pollakiuria Stranguria Dysuria

Diagnostic work-up

Laboratory examination

Biochemical evaluation

Biochemical evaluation has two aspects: evaluation of hepatocellular lesion by clinical enzymology and of hepatic function by hepatic function tests.

Clinical enzymology

Hepatobiliary enzymes have a high sensitivity for the detection of hepatobiliary disease, but must be interpreted with caution as they lack specificity (3). A part from hepatic disease, elevation also occurs by drug-induction (corticosteroids, anticonvulsants), metabolic (endocrinopathies), neoplastic, hypoxic, hypotensive, muscular and bone disease. Alanine aminotransferase (ALT) is a cytosolic relatively specific liver enzyme. The magnitude of ALT elevation is roughly proportional to the number of injured hepatocytes. Aspartate aminotransferase (AST), mitochondrial and cytosolic, is more sensitive, but less specific in detection of hepatobiliary disease as it is abundantly present within muscle cells. Alcaline phosphatase (ALP) is sensitive, but specificity is low because of the presence of numerous isoenzymes in the liver, kidney, intestine, bone, placenta and corticosteroid-induced isoenzyme. Canine liver ALP is produced by hepatocytes and located on hepatocyte canalicular membrane. GGT or γ-glutamyl transpeptidase, located on the hepatocyte canalicular membrane, is more specific but less sensitive than serum ALP. Elevations are most common with cholestatic disorders.

Hepatic function tests

Liver function parameters include albumine, urea, glucose, cholesterol, bilirubine, ammonia and bile acids (3).

Hypoalbuminemia is most frequently observed in chronic hepatic disease such as cirrhosis and congenital portosystemic disease. Hypoalbuminemia is not specific for liver disease, and may be encountered in protein-losing enteropathies and nephropathies, exudative cutaneous lesions and systemic inflammatory

disease.

Low serum urea nitrogen may be observed in cirrhosis and portosystemic shunting. In general, hypouremia is indicative of severe hepatic dysfunction affecting the urea cycle. Again, it is not specific for liver disease and may be observed in important diuresis, low protein intake or with congenital urea cycle enzyme deficiency.

Hypoglycemia is rather detected in animals affected by congenital hepatic abnormalities (portosystemic shunting or storage disease). It is more rarely observed in acquired hepatic insufficiency.

Hyperammonemia and ammonia tolerance test is very sensitive in detection of hepatic vascular abnormalities, but sample handling and proceeding is difficult (cold heparinized tubes, transport on ice, refrigerated centrifugation, assay within one hour) (3,11). Hemolysis may increase blood ammonia results. Hyperammonemia is not exclusively found in hepatic vascular disease in dogs, but also in other disease leading to hepatic insufficiency and urea cycle enzyme deficiencies (3).

Hyperbilirubinemia is less sensitive, but more specific then serum liver enzymes for the detection of hepatobiliary disease and may be prehepatic, hepatic and posthepatic.

Fasting and postprandial serum bile acids are efficient in the diagnosis of hepatobiliary disease, but do not allow distinction between different disease processes. Maltese dogs may have increased postprandial serum bile acids in the absence of hepatopathy.

Hematology

Hematologic changes include mild regenerative anemia (gastrointestinal bleeding, rarely spontaneous bleeding, see coagulation) or more frequently non regenerative (3). The latter is most often normocytic and normochromic (anemia of chronic disease). Non regenerative microcytic and hypochromic anemia suggests chronic gastrointestinal blood loss. Microcytosis has been described in hepatic vascular disease, chronic hepatitis and in dogs with acquired shunting secondary to cirrhosis. Leucocytosis and thrombocytopenia may be observed in chronic hepatitis (3,10).

Coagulation

Hepatocytes are responsible of production, activation, clearance and catabolism of almost all coagulation factors (3), thus coagulation abnormalities are quite common in dogs with chronic liver disease. Despite this fact, spontaneous bleeding in animals with hepatic disease is rare. Hemorrhage is more likely after provocative challenge (venipuncture, hepatic biopsy, etc). Commonly used tests include prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen and its degradation products (FDPs). Coagulation tests are essential before realizing hepatic biopsies (1,3). Plasma fibrinogen concentration seems to be the best predictor of bleeding tendencies. In general, coagulation tests are relatively poor predictors of an animal's bleeding tendency. Despite normal results of coagulation tests one should always assume that an animal with hepatic disease has higher than normal bleeding risk after provocative challenge.

Urinalysis

Urinalysis may reveal ammonium biurate cristalluria in dogs with portosytemic shunts (3).

Analysis of ascites

Table 3 summarizes the most common types of ascites encountered in hepatic disease in dogs (3, 12).

Table 3: Caracteristics of ascites and etiologic orientation in hepatic disease

	Pure transudate	Modified transudate	Exudate
Aspect	Clear, colorless	Serohemorrhagic	Serohemorrhagic, hemorrhagic, purulent
Specific gravity	< 1.015	1.015-1.030	> 1.025
Protein content g/L	< 15	15-30	> 25
Cell count (cells/µL)	< 1500	1000-7000	> 7000
Cell type	Primarily mesothelial cells and macrophages	Mesothelial cells, macrophages, neutrophils and lymphocytes	Primarily neutrophils
Etiologic orientation	Hypoalbuminemia, presinusoidal portal hypertension	Postsinusoidal portal hypertension, neoplasia	Peritonitis, neoplasia

Diagnostic imaging

Whereas clinical signs and laboratory testing allow suspicion and identification of hepatic disease, determination of the exact nature of the disease process requires diagnostic imaging and often histopathologic examination.

Abdominal radiographs

Abdominal radiographs allow assessment of liver size and opacity, presence of ascites (3,12). Microhepatia is observed with congenital vascular disorders and atrophic fibrosis and cirrhosis. Hepatomegaly may occur due to congestion, infiltrative disease or mass lesions. In dogs renomegaly may be observed in animals with portosystemic shunt. Mineralization may be detected in biliary lithiasis or some neoplastic, inflammatory, infectious or hemorrhagic processes.

Radiographic contrast imaging, such as mesenteric portography is less commonly performed nowadays to detect/localize portosystemic shunting because it is more invasive than ultrasonography.

Abdominal ultrasonography

Abdominal ultrasound enables evaluation of vasculature, focal or diffuse alterations in hepatic parenchymal and biliary disease, and realization of biopsies for histopathologic examination (1,3,12).
Indirect signs for hepatic disease, such as ascites may be detected. Bilateral nephromegaly and urolithiasis in a young dog may suggest presence of congenital vascular disease.
Hepatic parenchymal size, form, structure and echogenicity, as well as distribution of lesions (diffuse or focal) are evaluated. Metabolic, inflammatory, nodular, cystic and neoplastic lesions may be detected. Microhepatia is observed with congenital vascular disorders and atrophic fibrosis and cirrhosis. Absence of sonographic lesions does not exclude the possibility of hepatic disease. Few hepatic lesions have diagnostic sonographic features, in many cases hepatic histopathology is required for accurate diagnosis.
Ultrasonography in hepatic circulatory vascular disorders is very sensitive and specific for evaluation of portosystemic shunts, if realized by an experienced operator. Indirect and direct signs of secondary portosystemic shunts, arterio-venous fistula and portal hypertension may be seen.
Dilation of extra- or intrahepatic bild ducts and the cause of obstruction (intraluminal or extraluminal disorders) may be visualized. Abnormalities of the gallbladder wall and its contents may be identified.

Scintigraphy

Less available, scintigraphy is a sensitive mean of detecting portosystemic shunting. It may be considered if ultrasonography has failed to identify the presence of a shunt, but clinical signs and laboratory test results are consistent with shunting.

Computed tomography (CT) and magnetic resonance imaging (MRI)

CT and MRI may be of help in diagnosis of complex intra- and extrahepatic shunting (3). MRI may provide useful in differentiation of benign from malignant hepatic lesions (13).

Cytology and histopathology

Often required for definitive diagnosis, hepatic cytologic or histopathologic examinations are currently realized (3,12).
Ultrasound-guided hepatic fine needle aspirates (FNA) for cytologic analysis is easy to perform and mostly possible without anesthesia. Hepatic cytology is sensitive in detection of some neoplastic (particularly lymphoma) and reversible hepatocyte injury (vacuolar hepatopathy, etc).
Hepatic tissue samples may be obtained by blind, ultrasound-guided, laparoscopic or laparotomic biopsy. Histopathologic examination allows determination of the nature and extent of the disease and may provide a clue as to etiology. Special stains may indentify infectious agents or copper overload. Copper quantification may be realized on hepatic biopsies. Samples may be sent for bacterial culture if septic hepatitis is suspected. Cholecystocentesis may be realized if bacterial cholecystitis is suspected and severe mural abnormalities or biliary obstruction have been previously excluded.

Treatment of chronic liver disease in dogs

Treatment is reviewed in the lecture on treatment of chronic hepatic disorders in dogs.

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