Canine Hepatopathology: Clinical Manifestations, Pathophysiology and Diagnostic Considerations - A Review

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ABSTRACT

Hepatic diseases in dogs represent a complex group of disorders with diverse etiologies and manifestations. This paper reviews the current understanding of canine hepatopathology, including clinical symptomatology, underlying pathophysiological mechanisms and diagnostic considerations. The liver's remarkable regenerative capacity and its central role in metabolism make hepatic disorders particularly challenging to diagnose and manage in veterinary practice. Various clinical manifestations of hepatic diseases/disorders have also been dealt with in this paper. This review aimed to provide veterinary practitioners with an integrated understanding of canine liver diseases, from cellular injury mechanisms to clinical presentation patterns.

Keywords: Canine hepatopathology, Vacuolar hepatopathy, Hepatotoxicity

Liver diseases in canines present significant diagnostic and therapeutic challenges for veterinary practitioners. The complexity of hepatic disorders stems from the liver's multifaceted functions and its remarkable ability to compensate for injury until substantial damage occurs. As noted by Sumathi *et al*. (2017), liver diseases in canines are inherently complex, often difficult to diagnose. Understanding the intricate relationship between pathophysiological mechanisms and clinical manifestations is crucial for effective management of canine hepatopathology.

PATHOPHYSIOLOGICAL MECHANISMS OF HEPATIC INJURY AND HEPATIC RESPONSE TO INJURY

Hepatic cell injury can result from diverse causes, including physical trauma, infections, toxic substances, nutritional imbalances and immune system disorders (Wang, 2014). The fundamental mechanisms underlying cellular injury include ATP depletion, often due to hypoxia, damage to cellular membranes from oxygen-derived free radicals, disruptions in cellular metabolism and genetic damage. The liver responds to injury through three primary mechanisms, viz., adaptation, reversible injury and cell death (Zachary and McGavin, 2012).

Hepatocellular Adaptations

Hypertrophy and Hyperplasia: The initial response to hepatic injury often involves cellular adaptation through primary mechanisms like hypertrophy and hyperplasia (Zachary and McGavin, 2012). Hepatocytes undergo adaptation by increasing their size (hypertrophy) and number (hyperplasia). Hyperplasia, characterized by an increase in hepatocyte number, works synergistically with hypertrophy to preserve hepatic function during periods of increased demand or injury. These adaptive mechanisms demonstrate the liver's remarkable plasticity and ability to respond to varying physiological and pathological conditions (Fausto *et al*., 2006). Hepatocellular hypertrophy manifests as liver enlargement resulting from increased individual hepatocyte volume, achieved through expansion of intracellular organelles, including smooth endoplasmic reticulum, mitochondria and peroxisomes in response to physiological demands or chemical

stimulation (Klaassen and Amdur, 2013). This adaptive response occurs in response to physiological demands or chemical stimulations and represents the liver's attempt to maintain functional capacity despite ongoing stress (Klaassen and Amdur, 2013).

Vacuolar Hepatopathy: Vacuolar hepatopathy represents a spectrum of cytoplasmic vacuolation within liver cells, encompassing hydropic swelling, glycogenosis and steatosis (Peyron *et al*., 2015). Hydropic degeneration, characterized by enlarged hepatocytes with pale, finely vacuolated cytoplasm, results from impaired cellular homeostasis and water accumulation due to compromised regulation of water influx and efflux (Hoda and Hoda, 2020). Hepatic glycogenosis, associated with hyperadrenocorticism or glucocorticoid therapy, presents as enlarged hepatocytes with multiple cytoplasmic vacuoles and peripheral nuclear displacement. The presence of glycogen can be confirmed through magenta staining with the Periodic Acid-Schiff (PAS) method (Julian *et al*., 2015). Hepatocellular steatosis or fatty liver occurs in injured hepatocytes due to disrupted lipid metabolism, resulting in intracellular fat accumulation. This condition is characterized by small, discrete microvacuoles to large, coalescing macrovacuoles that displace the nucleus to the cell periphery (Cullen and Stalker, 2016).

Hepatocellular Atrophy: Hepatocellular atrophy results from a variety of injurious stimuli, including hypoxia, toxins, infectious agents, immune-mediated reactions and severe metabolic disturbances. Cellular death occurs through apoptosis or necrosis (Zeiss, 2003). Apoptosis represents a caspase-dependent, energy-requiring form of programmed cell death characterized by cellular shrinkage, preserved membrane integrity and fragmentation into apoptotic bodies subsequently phagocytosed by Kupffer cells and surrounding hepatocytes (Patel, 2000). These structural alterations are driven by the activation of caspases and endonucleases, which degrade structural proteins, DNA repair enzymes and DNA itself (Xia *et al*., 2017). Necrosis involves cytoplasmic swelling and loss of membrane integrity, eliciting an inflammatory response. Necrosis can be coagulative or liquefactive. Coagulative necrosis results from abrupt and severe protein denaturation, presenting as swollen hepatocytes with acidophilic cytoplasm, preserved cellular outlines and nuclear changes such as karyopyknosis, karyorrhexis or karyolysis. Liquefactive necrosis arises from osmotic swelling and cellular disintegration, leading to hepatocyte loss and replacement by erythrocytes and ceroid-laden macrophages (Van den Ingh *et al*., 2006). At times, a cell undergoing apoptosis may deplete its ATP reserves and result in secondary necrosis, resulting in swelling and lysis. Conversely, if the pathway for oncotic cell death is blocked, cellular stress may eventually push the cell toward apoptosis (Jaeschke *et al.*, 2004).

HEPATIC REGENERATION AND REPAIR

The liver possesses a remarkable regenerative capacity, capable of restoring up to two-thirds of its mass without functional loss. This regeneration involves coordinated proliferation of hepatocytes, bile duct epithelial cells, endothelial cells and sinusoidal lining cells. Acute liver injury with an intact structural framework heals completely through regeneration. However, chronic or severe damage that destroys the liver's architecture leads to scarring and abnormal repair patterns. Under persistent injury conditions, the liver attempts continuous regeneration but produces dysfunctional nodular tissue instead of normal architecture. These regenerative nodules, while substantial in size, fail to restore proper liver function due to disrupted blood circulation and bile flow, creating a paradoxical situation where increased tissue mass results in decreased functional capacity (Zachary and McGavin, 2012).

FIBROSIS AND CIRRHOSIS

Hepatic fibrosis represents a tissue repair response triggered by repeated liver injury, characterized by gradual accumulation of extracellular matrix, primarily collagens type I and III, resulting in fibrous scar tissue formation. The two distinct histopathological patterns observed include portal-based fibrosis associated with chronic hepatitis and bile duct diseases and central-based fibrosis linked to advanced fatty liver disease and impaired hepatic venous outflow (Majo *et al*., 2019; Pinzani, 2015). Cirrhosis represents the end-stage of chronic liver disease, characterized by widespread fibrosis and transformation of normal liver architecture into abnormal regenerative nodules. Key pathological features include fibrous septa bridging multiple lobules, regenerative hepatocyte nodules, and disrupted vascular organisation. These structural changes impair blood-hepatocyte exchange by increasing perisinusoidal extracellular matrix (Cullen and Stalker, 2016). Ductular reaction refers to the proliferation of reactive bile ductules triggered by liver injury. Pathologically, it is characterised by bile duct hyperplasia and is frequently observed in biliary diseases such as primary biliary cholangitis, primary sclerosing cholangitis, and biliary atresia (Sato *et al*., 2019).

CLINICAL MANIFESTATIONS OF CANINE HEPATOPATHOLOGY

General Clinical Signs: The clinical presentation of hepatic disease in dogs varies significantly depending on the severity and nature of liver damage. As noted by Cornelius and Bjoling (1992) and Anderson and Sevelius (1991), multiple signs exist in dogs affected with liver and biliary system diseases, including ascites and jaundice in chronic hepatitis cases. Verma *et al*. (2023) identified a range of clinical signs associated with hepatopathogenesis, including depression, weakness, nervous signs, jaundice, anorexia, vomiting, changes in spleen size, diarrhoea, emaciation, dark brown urine, pyrexia, polydipsia, polyuria, epigastric pain, ascites, coma, changes in liver size, altered stool color, haemorrhage and urticaria. While screening dogs presented with anorexia, lethargy, ascites, icterus, pigmented urine and vomiting, Sumathi *et al*. (2017) found that a significant number of animals with gastrointestinal disorders had concurrent liver diseases of different types, highlighting the frequency of hepatic involvement in canine illnesses.

Breed-specific Considerations: Some dog breeds show predisposition to specific types of hepatic disease. Watson (2004) noted that some cases of chronic hepatitis were associated with primary or secondary increases in copper (copper disease), while others were autoimmune in nature. Based on current evidence, the most likely breeds to have autoimmune hepatitis are Cocker Spaniels, English Springer Spaniels, and some Dobermans.

Acute vs. Chronic Hepatitis: Acute or chronic hepatitis is determined by histological examination of liver biopsy specimens. The activity of inflammation is determined by the amount of hepatocellular necrosis and swelling, whereas chronicity is determined primarily by the extent of fibrosis and regeneration. Acute hepatitis presents a moderately severe disease that may recover completely, though in very severe cases, disseminated intravascular coagulation and bleeding might occur (Rothuizen, 2009). The clinical picture depended entirely on the severity of liver damage and might vary from insignificant to fulminant lethal disease. Chronic hepatitis presents more insidiously, with some affected dogs being asymptomatic at presentation. Clinical signs might be inapparent in animals with compensated advanced disease (Watson, 2004). However, when symptomatic, chronic hepatitis cases typically have ascites, jaundice, vomiting and diarrhoea.

Hepatic Encephalopathy: Hepatic encephalopathy may occur in chronic hepatitis cases, revealing nervous system-related symptoms. Dixit *et al*. (2010) identified nervous signs like ataxia, hypersalivation, head pressing, seizures and behavioural changes associated with cirrhosis or intrahepatic portosystemic shunt. Rothuizen (2009) noted that hepatic encephalopathy in fulminant hepatitis was characterized by high blood ammonia values.

SPECIFIC DISEASE ENTITIES

Infectious Causes

Leptospirosis: Leptospirosis in dogs can cause hepatitis, leading to liver damage and potentially liver failure, manifested as jaundice, liver failure or other severe liver complications. Joseph *et al*. (2023) linked leptospirosis in dogs with signs of hepatic disease. McCallum *et al*. (2018) emphasized that the presence of hepatic leptospiral organisms might be associated with chronic granulomatous hepatitis without clinical evidence of renal involvement, highlighting the link between chronic hepatitis and leptospirosis.

Infectious Canine Hepatitis: It is a systemic disease caused by canine adenovirus type 1 (CAV-1), genetically and antigenically distinct from CAV-2 associated with respiratory disease. In affected dogs, the symptoms found are fever, inappetence, diffuse haemorrhages, abdominal pain, vomiting, diarrhoea and less frequently dyspnoea. Corneal opacity and interstitial nephritis might occur in 1-3 weeks after clinical recovery, due to circulating immune complex deposition (Decaro *et al*., 2007).

Other Infectious Agents: Acute hepatitis can result from various infectious agents, including viruses (canine adenovirus-1, herpesvirus), bacteria (Leptospira, *Clostridium piliforme, Helicobacter canis*) and protozoa (*Toxoplasma gondii)* (Suriawinata and Thung, 2006).

Neoplastic Conditions

Liver tumours in dogs can be either primary or secondary, with secondary neoplasms being more common, with 129 secondary and 49 primary in a study conducted by Trigo *et al*. (1982). Among primary tumours, 14 were benign (8 hepatocellular adenomas and 6 cholangio cellular adenomas) and 35 were malignant (18 hepatocellular carcinomas, 13 cholangio cellular carcinomas, one combined hepatocholangio cellular carcinoma, 2 haemangiosarcomas and one fibrosarcoma). Among secondary liver tumours, lymphosarcoma was the most frequent (67 cases), followed by splenic haemangiosarcoma (15 cases) and pancreatic carcinoma (9 cases). Clinical symptoms vary depending on tumour severity and extra pancreatic neoplasms, including neuroendocrine tumours, hepatocellular carcinoma, hepatoma, hemangiosarcoma, leiomyoma and leiomyosarcoma could cause hypoglycaemia through insulin or insulin analogue secretion, increased glucose utilization or impaired hepatic glucose homeostasis (Dorn *et al*., 2021).

Metabolic Complications

Hypoglycaemia: Low glucose levels can be extremely dangerous in dogs and require immediate treatment. Hypoglycemia and related signs may occur not only from malnutrition but also from insulinoma, chronic renal failure, severe infection or sepsis, hyperpituitarism and Addison's disease. Liver failure and liver cancer can lead to hypoglycaemia in dogs (Fernandez *et al*., 2009). Clinical signs of hypoglycaemia result from both decreased glucose supply to the brain and stimulation of the counter-regulatory sympathoadrenal system.

Toxic Hepatopathy: Hepatotoxicity might result from natural and synthetic substances, including metals (iron, copper), medicines (acetaminophen), plant toxins, fungal metabolites (mycotoxins), bacterial products such as microcystin-LR and industrial

chemicals, particularly aromatic solvents (Klaassen and Amdur, 2013). Many commonly used medicines are known for their hepatotoxic potential. Ketoconazole, an antifungal agent, is among the most frequently implicated drugs, causing dose-dependent hepatocellular injury. Carprofen and other non-steroidal anti-inflammatory drugs, such as meloxicam, have been associated with idiosyncratic hepatotoxicity in dogs. Phenobarbital, widely used as an anticonvulsant, can cause chronic hepatotoxicity on prolonged use, often leading to vacuolar hepatopathy and fibrosis. Trimethoprim-sulfamethoxazole has been linked to cholestatic and hepatocellular injury in dogs. Azathioprine, an immunosuppressive agent, and lomustine, a chemotherapeutic drug, are also recognised hepatotoxins in canines. Additionally, tetracyclines and certain anthelmintics such as mebendazole had been reported to cause hepatic injury in dogs (Trepanier, 2004). Toxic liver injury may manifest in cytotoxic, cholestatic or mixed forms. Cytotoxic injury results in hepatocellular degeneration, zonal or focal necrosis, apoptosis or steatosis. Cholestatic injury reflects impaired bile flow due to canalicular or biliary epithelial damage, presenting clinically as obstructive jaundice. Mixed injury combines features of both hepatocellular damage and cholestasis, and chronic toxic liver damage can lead to chronic hepatitis, progressive fibrosis, cirrhosis, veno-occlusive disease or neoplasia, depending on the nature and duration of toxic exposure (Bashir *et al*., 2018).

DIAGNOSTIC CONSIDERATIONS

Understanding the coordination between liver-related clinicopathological changes is crucial for diagnosis. Key laboratory abnormalities include elevated total bilirubin, hypoproteinemia, decreased blood urea nitrogen, total cholesterol and aspartate aminotransferase (Rothuizen, 2009). Elevated AST levels in liver diseases indicate liver damage, but AST is not as specific for liver injury as alanine aminotransferase due to AST's wide distribution in organs, including intestines, placenta, liver, kidney and bone. Muscle injuries, red blood cell destruction and *ex vivo* hemolysis can also lead to AST elevation in canines (Solter, 2005).

Liver biopsy using a Vim-Silverman needle or Tru-cut biopsy needle, followed by histopathological examination, is of considerable diagnostic value in the confirmation of acute or chronic hepatitis. Histopathology enables a detailed assessment of hepatic architecture, degree of inflammation, fibrosis, necrosis and aetiology, making it particularly valuable for diffuse hepatic lesions. However, it has some disadvantages, including the risk of haemorrhage, especially in patients with coagulopathy, difficulty in obtaining representative samples from focal or multifocal lesions, and the requirement for either sedation or general anaesthesia (Rothuizen and Twedt, 2009). Ultrasonography is an essential non-invasive adjunct in the diagnosis of hepatic diseases, enabling evaluation of hepatic size, echogenicity, parenchymal texture and the detection of focal lesions, biliary abnormalities and portal vascular anomalies. It also facilitates ultrasound-guided fine-needle aspiration and biopsy (Nyland and Mattoon, 2015). Laparoscopy is a useful diagnostic modality, as it allows direct visualisation of the hepatic surface and permits targeted biopsy collection under visual guidance, thereby improving sample quality compared to blind percutaneous techniques (Richter, 2001).

Analysis of GGT, serum bile acids and bilirubin levels - comprising both conjugated and unconjugated fractions - in live dogs is generally of high diagnostic value in cases of hepatic involvement due to multiple etiological complexes. In particular, serum bile acid estimation is considered one of the most sensitive and reliable indicators of hepatic functional capacity and portosystemic

shunting, as bile acids are exclusively synthesised in the liver, conjugated, secreted into bile, and reabsorbed via enterohepatic circulation. Any disruption in this pathway results in elevated serum concentrations, making pre and post-prandial bile acid assays highly informative in suspected hepatobiliary disease (Center, 1993).

SUMMARY

Canine hepatopathology encompasses a complex spectrum of diseases with varied etiologies, pathophysiological mechanisms and clinical presentations. The liver's remarkable regenerative capacity often masks early disease, making diagnosis challenging until significant damage occurs. Understanding the intricate relationships between cellular injury mechanisms, adaptive responses and clinical manifestations is essential for effective diagnosis and management of hepatic disorders in dogs. The integration of clinical symptomatology with underlying pathophysiological processes provides a comprehensive framework for understanding canine liver disease. Future research may focus on developing more sensitive early diagnostic markers and targeted therapeutic approaches to improve outcomes in dogs with hepatic disorders. Veterinary practitioners may maintain a high index of suspicion for liver disease in dogs presented with nonspecific clinical signs.

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