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Liver and Lipid Disorders

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Disease of the avian hepatobiliary system is frequently diagnosed in clinical practice.

Primary conditions include infection from a variety of agents, toxic insults, nutritional disorders and neoplasia. Diagnosis of hepatic disease can be challenging, especially when it occurs concurrently or secondarily to other problems. The liver also has an important role in the metabolism and storage of lipid and a number of hepatic conditions are often caused by or intertwined with aberrations in lipid metabolism. The focus of this paper is the development and impact of excessive lipid within the liver.

The liver has a central and critical role in the metabolism and regulation of carbohydrate, fat and protein. The additional functions of the liver that are ultimately a consequence of these processes include the regulation and storage of glucose; detoxification and processing of metabolic waste; detoxification of toxins and metabolism of drugs; and the formation of proteins and amino acids that are essential for the synthesis of hormones, coagulation factors, carrier proteins and enzymes. Other roles the liver has include immune activity and the storage of vitamins (A, D, K) and trace minerals (iron, copper). As a result of the number and complexity of liver functions, many pathways can become impaired when the liver is functioning sub-optimally.

Clinical signs of hepatic disease

Symptoms of hepatic disease can be subtle, nonspecific and highly variable due to enormous number of functions the liver is involved. Table 1 lists a number of clinical signs and features that have been reported in avian liver disorders (Lumeij, 1994; Hochleithner et al., 2006; Grunkemyer, 2010; Nemeth et al., 2016). Table 2 details a number of potential aetiologies for hepatic disease, where clinical signs can also be dictated by the type, severity and chronicity of the disease process (Lumeij, 1994; Hochleithner et al., 2006; Grunkemyer, 2010).

Diagnosis of hepatic disease

Haematology, biochemistry and radiography remain the mainstay for detection of liver pathology. Detection of hepatomegaly, microhepatica, hepatic inflammation or dysfunction however, does not establish a definitive diagnosis. A suspected diagnosis can be supported by non-invasive methods, such as testing for specific pathogens. Ultrasonography and advanced imaging (CT, MRI) can also be useful (Grunkemyer, 2010), especially in cases of suspected hepatic neoplasm where guided needle aspiration can be performed.

The definitive diagnosis is best achieved by liver biopsy. This can be performed endoscopically or via open laparotomy. Tissue samples are collected for histopathology and microbial culture. Additional samples should be collected to be frozen if PCR for specific pathogens and toxicology are required.

While mild elevations in lipid may be seen in dietary excess, severe hyperlipidaemia without hepatic involvement may warrant further investigation for reproductive disease, neoplasia and thyroid dysfunction.

Lipid metabolism

The three sources of lipid in the liver are derived from dietary fats, dietary carbohydrates and from adipose tissue (Butler, 1976; Buyse et al., 2015).

1. **Exogenous (dietary) lipid metabolism**

   Most dietary lipids are triglycerides, with the remainder being cholesterol esters, phospholipids and fatty acids. Digestion of dietary lipid starts with emulsification in the ventriculus. Partial hydrolysis occurs in the small intestine by lipases and some of the resultant free fatty acids are

absorbed directly in the small intestines. Most of the free fatty acids however, form micelles with bile salts and are resynthesised to triglycerides within the enterocyte. They are then combined with phospholipids, cholesterol, fat soluble vitamins and apiloproteins to form lipoproteins. These lipoproteins travel to the liver via the portal circulation and are therefore referred to as portomicrons. Although they are transported to the liver, they are primarily oxidised by other tissues, such as adipose and muscle (Buyse et al., 2015).

2. **Endogenous lipid metabolism**

The liver is primarily responsible for the synthesis of lipid from non-lipid precursors (protein and carbohydrate). VLDL, LDL and HDL refer to lipoproteins of various cholesterol and triglyceride content. They are formed by the liver to transport these lipids to tissues and circulate until they are taken up or cleared by the liver. In adipose tissue, the lipoproteins are hydrolysed, the lipid re-synthesised as triglycerides and stored. This process is regulated by lipoprotein lipase. Mobilisation of adipose triglycerides to fatty acids occurs during stress or starvation. The skin is another source of lipid in birds can explain the development of xanthoma and xanthomatous change in response to inflammation (Pass, 1989).

Dyslipidaemia

Aberrations in lipid metabolism are a feature of hepatic dysfunction and both hyperlipidaemia and hypolipidaemia can be reported (Hochleithner, 1994). Hypolipidaemia may occur if the liver is unable to synthesise lipids, proteins for lipid transport or bile acids for intestinal absorption. Hyperlipidaemia however, is often a feature of cholestatic hepatic disease and may occur concurrently with elevations in bile acids. Other causes of hyperlipidaemia in birds include reproductive activity in hens, hypothyroidism, genetic factors, renal disease, pancreatic disease and diabetes mellitus (Hochleithner, 1994).

Hepatic steatosis

Hepatic steatosis is the excessive accumulation of fat in the liver. This process can eventually disrupt the functions of hepatocytes or cause inflammation, leading to a variety of clinical manifestations. A number of disease syndromes, secondary to hepatic steatosis have been reported in poultry (Butler, 1976). These disorders appear to be multi-factorial conditions with dietary imbalances and restricted exercise playing major roles (Butler, 1976). During reproduction, female birds undergo significant hepatic lipogenesis stimulated by the ovarian oestrogen. Approximately half of the lipid content in the liver is required for each egg (Butler, 1976). Chronic reproductive abnormalities causing excessive oestrogen production can therefore lead to hepatic steatosis.

Hepatic steatosis can develop from a number of mechanisms that include:

1. Increased lipogenesis
   - Increased lipogenesis occurs with an increase in dietary carbohydrates. Carbohydrates provide precursors and enzyme cofactors for fatty acid synthesis. The high carbohydrate diet of many parrots is therefore a major factor in the development of hepatic steatosis.
   - Studies in poultry have shown that high dietary fat inhibits fatty acid synthesis in the liver by feedback on lipogenic enzymes, although deficiencies in essential fatty acids (linoleic and arachidonic) increases hepatic lipogenesis.
2. Decreased transport of lipids from the liver
   - Decreased transport of lipids from the liver occurs with deficiencies in protein and nutrients that contribute to the phospholipid component of lipoprotein. Diets low in amino acids or nutrients, such as methionine, folic acid or vitamin B12 have been implicated in arresting lipid transport from the liver, result in accumulation of lipid in hepatocytes.
3. Decreased deposition of lipid in adipose
   - The uptake of lipid into the adipocytes can be reduced by the inhibition of lipoprotein lipase. ACTH and glucagon lead to the production of cyclic AMP that results in inhibition of this enzyme. Stress has been implicated as the precursor to this process.
4. Decreased oxidation of fatty acids in tissues
   - A decrease in lipid catabolism can occur with dietary deficiencies in vitamins and minerals that contribute to lipolytic enzyme co-factors.

Hepatic steatosis may be suspected in pet birds based on a history of poor diet and limited exercise. Other supportive features can be clinical findings such as obesity and biochemical abnormalities in hepatic enzymes, lipid and bile acids. Definitive diagnosis of hepatic steatosis is best achieved by histological examination of liver biopsy samples.

Hepatic lipidosis

The term hepatic lipidosis is often used interchangeably with hepatic steatosis or fatty liver syndrome when re-

porting liver disease in birds. Mammals differ from birds in that the majority of lipogenesis occurs in adipose tissue. Hepatic lipidosis in mammals is described as a negative energy balance state with features are similar to hepatic steatosis but also including an overwhelming influx of fatty acids from the adipose tissue (Valtolina, 2017). It is for this reason that hepatic lipidosis may best be used in circumstances of acute overwhelming mobilisation of lipid due to starvation, rather the chronic process of steatosis that is often seen in birds.

The liver is a vital organ with multiple roles in metabolism, hormone production and critical functions like coagulation. The extensive list of potential causes of hepatic disease can make diagnosis challenging. It is important to definitely diagnose and define the problem in order to provide appropriate therapies.

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Table 1. Clinical Signs of Avian Liver Disorders
Abnormal bleeding - spontaneous haemorrhage, poor clotting ability, melena, epistaxis
Non-specific - lethargy, anorexia, diarrhoea
Biliverdinuria, bilirubinaemia
PUPD
Coelomic distension - hepatomegaly, ascites
Dyspnoea - hepatomegaly, ascites, hepato-pericardial effusion
Abnormal beak, nails and feathers - dull, abnormal pigmentation, flaking keratin, excessive keratin growth
Haemorrhages in nail and beak
Stunted growth
Feather destructive behaviours
Sudden death - hypoglycaemia, fatal hepatic haemorrhage

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Table 2. Aetiology of Hepatic Diseases		
Infectious agents	**Bacterial**	*Chlamydia psittaci* *Mycobacteria* *Mycoplasma* *Streptococcus, Enterococcus,* *Pseudomonas, Salmonella, E.coli* *Yersinia pseudotuberculosis*
	Fungal	*Aspergillus* *Candidia*
	Viral	Circovirus Polyomavirus Herpesviruses Adenoviruses Reovirus
	Protozoal	*Atoxoplasma* *Trichomonas* *Leucocytozooan* *Plasmodium*
	Parasitic	Trematodes Nematodes
Degenerative	Amyloidosis Portal hypertension, secondary to right-sided heart failure	
Toxin	Mycotoxins Pesticides Hepatotoxic drugs	
Neoplasia	Lymphoma Adenocarcinoma Haemangiosarcoma Metastatic disease	
Nutritional	Hepatic steatosis Hepatic lipidosis Iron storage disease	