ZOOLOGY AND VETERINARY MEDICINE

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DIAGNOSTIC TESTS OF JAUNDICE IN CATS AND DOGS

Abstract. *Jaundice is a condition in which the skin, whites of the eyes and mucous membranes turn yellow because of a high level of bilirubin, a yellow-orange bile pigment. Jaundice has many causes, including hepatitis, gallstones and tumors. Bile is fluid secreted by the liver. Bilirubin is formed from the breakdown of red blood cells. There are three types of jaundice: mechanical, parenchymatous and hemolytic. The prognosis depends upon the underlying cause.*
Keyworlds: *jaundice, icterus, enzyme*

Jaundice is a syndrome characterized by yellow colouration of visible mucous membranes (gums), sclera and unpigmented skin; accumulation of excess bilirubin, bile acids and their salts in the blood; resulting in nervous disorders, cardiovascular and digestive systems, as well as skin itchy. Icterus is also known as jaundice or yellow jaundice. Icterus is not a disease; it is a clinical sign indicating that an underlying disease is present. When the underlying disease is diagnosed and treated successfully, icterus will resolve. Normal serum bilirubin levels should be less than ~ 6 μmol/L and jaundice only becomes visible when levels are around 35 μmol/L. [2]

The degree of jaundice depends on the degree of bilirubinemia. The stable pale-yellow colour of the conjunctiva indicates an increase in the content of unconjugated (indirect) bilirubin in the blood, and the intense yellow (from orange-yellow to brown-yellow) indicates an increase in conjugate (direct) bilirubin. Jaundice is most noticeable in places where skin is thin and less pigmented - the inner surfaces of the auricular shells and thighs. Since most of a cat`s or dog`s skin is covered by fur, jaundice is most easily seen in the gingivae (gums), the sclerae (white part of the eyes), and the pinnae (ear flaps). Jaundice may be difficult to detect in cats and dogs

that have pigmented (dark) gums or skin. However, the jaundice of the skin is particularly noticeable in dogs and cats, much less in cattle, sheep and pigs. In other species, it can only be observed in mucous membranes. [3]

There are three main types of jaundice: prehepatic, hepatocellular, and post-hepatic. Prehepatic icterus occurs when the rate of production of bilirubin exceeds the ability of the liver to excrete it. Parenchymatous jaundice is caused by disruption of bilirubin absorption in hepatocytes, conjugation with glucuronic acid and secretion into the bile tubules in case of liver diseases (hepatitis, hepatosis, cirrhosis). Posthepatic icterus occurs if the liver is able to clear the normal daily bilirubin load into the biliary system but the biliary system is unable to excrete it via the GI tract. This may be seen with biliary obstruction (e.g., severe pancreatitis) or biliary system rupture. [6]

Table 1

Types of jaundice	**Urine**		**Faeces**	**Blood**		
	Bilirubin	Urobilinogen	Stercobilin	Direct bilirubin	Indirect bilirubin	Ratio of direct bilirubin to total
Prehepatic	0	↓ or N	↑	N	↑	0,2
Hepatic	+	↑	↑,0,N	↑	↑	0,2-0,7
Posthepatic	+	↓ or N	↓	↑	↑	0,5

Some of the causes of liver-related icterus include infectious diseases (feline leukemia virus (FeLV), feline infectious peritonitis (FIP), fungal diseases, neoplasia or cancer, hepatic lipidosis (fatty liver syndrome), cholangiohepatitis complex, prolonged anorexia, ingestion of toxins Jaundice can be also caused blood parasites, heartworms, expansion of the liver, viral or bacterial infection, chemical exposure (leads to toxic hepatopathy), pancreatic cancer, cancer of the gall bladder, hepatic liplipidosis (liver fatty), lymphoma (cancer), cholangiohepatitis (inflamed bile ducts or liver) and hepatic amyloidosis (accumulated amyloid in the liver). [5]

A complete physical examination, including body temperature, pulse, respiratory rate, fundic examination, cardiovascular auscultation, and abdominal palpation, is essential. Physical findings may indicate potential underlying

etiologies, such as hepatomegaly with hepatic lipidosis, cranial abdominal discomfort with pancreatitis, and tachycardia with anemia. The physical examination is often dominated by the color of the cat. Icterus is best appreciated as a discoloration of the mucous membranes, the sclera, and/or the inner aspect of the pinnae. The intensity and actual color may be influenced by the normal tissue color, degree of anemia, and perfusion. Occasionally, a blood sample is drawn for some other reason and the serum is noted to be yellow before the cat becomes visibly jaundiced. In these cases, the yellow serum is usually an indication of impending problems, and your veterinarian will recommend a complete diagnostic work-up.

The first goal should be to determine if the icterus is prehepatic, hepatic or posthepatic. The diagnosis of prehepatic icterus is relatively straightforward as the patient will be at least moderately anaemic. A PCV is thus always the first test to prioritise in icteric patients. If the animal is moderately or markedly anaemic (approx PCV 25% in dogs, PCV 20% cats), then the icterus is very likely to be prehepatic in origin and differential list and work-up for haemolytic anaemia should be pursued.

In patients with mild anaemia, the situation is less clear-cut as a mild anaemia may be associated with several causes of hepatic and posthepatic icterus. Clinical judgment must then be used but hepatic or posthepatic icterus is more likely. If prehepatic icterus is ruled out, then a biochemistry panel and ultrasound imaging of the abdomen should be performed. The information gained from ultrasound imaging of the abdomen will be variable dependent on the skill of the ultrasonographer but at a minimum the animal should be assessed for the presence of free abdominal fluid and if present this should be sampled.

With increasing skill level, the liver parenchyma should be examined and the pancreas, gall bladder and bile duct assessed. The diagnosis of obstructive cholestasis involves measurement of the diameter of the common bile duct with and identification of dilation - this requires a high level of skill.

Your veterinarian will perform a test called a CBC or Complete Blood Count. The CBC measures the number of red blood cells, white blood cells, and platelets (important for normal blood clotting). If an automated machine is used to perform the CBC, the red blood cells will be measured by a direct red blood cell count. As

part of the CBC, tests called the PCV (Packed Cell Volume) and/or the hematocrit will determine the proportion of the blood that is red blood cells. Evaluation of a CBC is critical in jaundiced patients because of the inter-relationship between red blood cells and the liver, as explained above. The CBC will document the presence and severity of anemia by providing an evaluation of the total red blood cell numbers, the total hemoglobin, and the packed cell volume (PCV) of the blood sample. The CBC (complete blood count) may indicate the presence of inflammation or infection within the liver and/or gall bladder by an increased white blood cell count. Anemia, if present, is usually very mild, and differs in character from the more severe anemia associated with red blood cell destruction or hemolysis. The presence of certain shape changes in red blood cells is supportive of underlying liver disease. These measurements will indicate whether the cat or dog are anemic. Other components of the CBC will help determine whether the anemia is caused by hemolysis, including an examination of a blood smear to look for immature red blood cells, abnormal red blood cells, or unusual clumping of cells. Slow sedimentation rate of erythrocytes in animals is less frequent and is observed in diseases accompanied by fluid loss and blood clotting (diarrhea, polyuria), mechanical and parenchymal jaundice, stachybotoxicosis, colic, cardiac decompensation. When examining a cat with jaundice, a simple method such as hematocrit and serum protein concentration is key to the diagnosis.

Anemia often dominates the clinical picture in these cats, but overall it seems that cats are better able to tolerate lower levels of hematocrit than dogs. If the hematocrit / common protein and CBC indicate that hemolysis is not the cause of increased bilirubin, then our attention is drawn to the liver and gallbladder as the cause of yellowing of the skin in cats. Then, biochemical analysis will reveal an increase in the concentration of total bilirubin (usually above 2.5-3.0 mg/dL in the absence of yellow skin). Changes noted microscopically on the blood smear may also give us information regarding the mechanism or cause of the red blood cell destruction. For example, the appearance of large numbers of dense, rounded red blood cells called spherocytes are supportive of immune-mediated destruction of red blood cells. Similarly, the clumping or agglutination of small groups of red blood

cells is suggestive of immune-mediated destruction of red blood cells. The presence of small ‘bubbles’ at the edge of red blood cells (Heinz bodies) suggests that membrane damage to the red blood cells has occurred and may be resulting in their accelerated destruction because of increased fragility. Occasionally the presence of red blood cell parasites such as Mycoplasma hemofelis is detected on the outer membrane of a cat’s red blood cells. The presence of this parasite will result in the accelerated removal of red blood cells from circulation. In addition to hyperbilirubinemia, cats with mycoplasmosis are frequently hyperglobulinemic as a result of chronic immune stimulation, and they may have mild to moderate elevations in liver enzyme activity as a result of anemic–hypoxia-induced hepatocyte necrosis. [4]

The serum biochemistry profile contains many tests that are helpful in the diagnosis of liver disease. However, it must be stressed that although changes in the biochemistry profile may support the diagnosis of liver disease, they will rarely indicate the exact cause. The major feature noted on the serum biochemistry profile when increased red blood cell destruction is the cause of jaundice is an increase in the serum bilirubin concentrations (hyperbilirubinemia). Mild changes in the liver related enzymes may be evident as a consequence of increased bilirubin levels. A biochemistry profile, which is a group of 10-30 tests, is performed on a blood sample from the cat with icterus. The biochemistry profile contains several tests that are specific for liver disease. The main liver enzymes are alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin. In some cases, your veterinarian will also recommend a bile acid analysis, which assesses liver function. ALT is a hepatocellular enzyme whereas AlkP is localized to the biliary endothelium. Thus with hepatic disease, the ALT tends to be proportionately higher than the AlkP and with posthepatic icterus, this is reversed. Other points it is important to remember are that neither ALT nor AlkP are reflective of liver function and in fact with some late stage chronic liver disease they may actually start to fall as the liver mass remaining to release them is so reduced. Destruction of individual liver cells (hepatocytes) is indicated by increases in the liver enzymes ALT and AST. Such hepatocyte destruction may occur due to many

causes including toxins, infectious diseases (bacterial and viral), alterations in liver blood flow, and tumors. The destruction of large numbers of individual hepatocytes either may impair the ability of the liver to process bilirubin, or may impair the flow of bile within the liver. Cholestasis or blockage of bile flow within the liver or from the gall bladder to the intestine will result in increases in other liver related enzymes, namely ALP (alkaline phosphatase) and GGT (gamma-glutamyltransferase). Alkaline phosphatase (ALP) in cats is an indicator of severe primary liver disease, unlike dogs that have alanine amino transferase (ALT) as a specific indicator of liver disease. ALP in cats has a short half-life (6 hours), is present in deficit and is not induced by glucocorticoids, so a much smaller increase in this indicator should serve as a warning, unlike dogs. No less informative enzyme in cats is gamma-glutamyl transpeptidase (GGT), especially in cases of inflammatory liver diseases, as this enzyme is concentrated in the bile ducts. [1]

The other parameters it is vital to assess on a biochemistry panel are those that are indicators of poor liver function notably blood glucose (low with hepatic failure as glucose is produced in liver via gluconeogenesis), BUN (low with hepatic failure as BUN is produced in liver from excess protein via urea cycle), cholesterol (low in hepatic failure as synthesized in liver) and albumin (low especially in chronic hepatic failure as synthesized in liver). If hepatic failure is suspected, clotting times (PT and PTT) should also be evaluated. Hepatic failure leads to prolongation of clotting times as most of the clotting factors are synthesized in the liver. [6]

Occasionally immune-mediated destruction of red blood cells is suspected, but cannot be definitively confirmed with the above screening tests. In this instance, a Coombs' test, which is a test to detect the presence of antibodies on the surface of the red blood cells, may be performed. If infectious agents are suspected to be a cause of the hemolysis, then specific tests for their detection may be recommended. Such tests may require submission of blood to a referral laboratory, and include Mycoplasma hemofelis, feline leukemia virus and Ehrlichia. [6]

A urinalysis will confirm the presence of hyperbilirubinemia by documenting increased amounts of bilirubin in the urine sample. Furthermore, the urinalysis may provide us with information regarding the site of red blood cell destruction, and may

show whether any damage to the kidneys has occurred as a result of the red blood cell destruction. In liver diseases, the number of ketone bodies in blood and urine increases sharply. To evaluate the protein-synthetic function of the liver the content of total protein and its fractions is determined. Excretor function is determined by the introduction of bromophenol blue or bromosulfalein into the blood.

Diagnosis of triaditis is based on identification of disease in each of the 3 tissues involved; the gold standard for diagnosis is histopathology. Less invasive diagnostics include the feline pancreatic lipase immunoreactivity (fPLI) blood test, abdominal ultrasound, liver FNA, cholecystocentesis, cytology, culture and sensitivity, and small intestinal endoscopic biopsy; however, these patients may have increased anesthetic risks. Although not widely available in private practice, feline abdominal laparoscopy can be performed with equipment sized for pediatrics and allows the collection of tissue for histopathology (liver and pancreas) as well as direct aspiration of the gallbladder

The absence of significant anemia suggests that the liver, not increased red blood cell destruction, is the cause of the jaundice. These blood tests will indicate that liver disease is present, but not its cause or whether it is reversible. To make that determination, a study of liver tissue (biopsy) or liver cells (cytology) is necessary. This can be done in one of three ways:

1. Fine-needle aspirate and cytology

To perform this procedure, a small gauge needle is inserted through the skin into the liver. A syringe is used to aspirate some cells from the liver. The cells are placed on a glass slide, stained and studied under a microscope. This is the least invasive and quickest test, but it has certain limitations. Because only a few cells are obtained, it is possible that a representative sample from the liver will not be obtained. It is also not possible to view the cells in their normal relationship to each other. [7]

2. Needle biopsy

This procedure is similar to the fine-needle aspirate except a larger biopsy needle is used. Often, this test is performed during an ultrasound examination and is

called an ultrasound-guided needle biopsy. The needle biopsy gives a core of tissue, not just a few cells. The sample is fixed in formaldehyde and submitted to a pathologist for analysis (a technique called histopathology). Tissue and fluid from lesions in the liver or gall bladder might be sent to a veterinary referral laboratory for bacterial culture (this determines what types of bacteria, if any, are present). General anesthesia is required, but the cat is anesthetized for only a very short time. The core biopsy allows the pathologist to view the cells in their normal relationship to each other. However, the veterinarian cannot choose the exact site of the liver to biopsy because the liver is not visible. Therefore, it is still possible to miss the abnormal tissue.

3. Surgical wedge biopsy

The cat is placed under general anesthesia, and the abdomen is opened surgically. This permits direct visualization of the liver and the surgeon can choose the exact site for biopsy. A piece of the liver is surgically removed using a scalpel. This approach gives the most reliable biopsy sample.

4. Ultrasound examination

The gall bladder and bile ducts must be examined to confirm the presence of an obstruction. Although this may be possible using radiographs (x-rays), an ultrasound examination is a more accurate non-invasive way to evaluate the gall bladder and bile duct. Exploratory surgery is occasionally necessary to properly evaluate the cat for biliary obstruction. [7]

The pancreas may be evaluated at this time to ensure that inflammation or masses within this nearby organ are not affecting liver or gall bladder function. Radiographs may be used either instead of or in addition to ultrasound evaluation. If free abdominal fluid has been identified on ultrasound examination and sampled, then a bilirubin should be run on this fluid. Biliary system rupture is diagnosed when the bilirubin in the free abdominal fluid is higher than the serum bilirubin. Fluid within the abdomen may be a consequence of underlying liver or gall bladder disease. A sample of this fluid should be submitted to a veterinary pathologist for cytological analysis.

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