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# Bilirubin encephalopathy (kernicterus) in an adult cat

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## Abstract

*Case summary* An adult cat presented with neurological signs and marked icterus. Clinical pathology tests detected increased serum alkaline phosphatase levels, as well as alanine aminotransferase, total bilirubin, unconjugated bilirubin and conjugated bilirubin above the normal reference intervals. Ultrasonography showed hepatomegaly and a dilated gall bladder. Following these results, the cat was referred for a cholecystectomy owing to a clinical suspicion of obstructive cholecystitis. The animal died in the postoperative period and was referred for necropsy. Grossly, the animal had marked icterus. On the cortical surface and in the brain parenchyma there were marked yellowish areas. The liver was diffusely reddish-orange, enlarged and the capsular surface was slightly irregular. The gall bladder was absent. At its anatomical site and surrounding the common hepatic duct, a whitish nodular neoplasia of 2.0 cm was found. Microscopically, a cholangioma was diagnosed in the region of the common hepatic duct. In the white matter of the cerebellar vermis, there was axonal degeneration associated with gliosis. In the Purkinje neuron layer there was slight multifocal necrosis. Some neurons contained amorphous and brownish pigment (bilirubin) in the cytoplasm. Clinical and pathological findings indicated hepatic and post-hepatic icterus from obstructive cholangioma, resulting in kernicterus.

*Relevance and novel information* Kernicterus is a neurological disorder that is rarely diagnosed in animals, especially in adults. This report provides evidence that kernicterus can occur in adult cats, secondary to increased unconjugated and conjugated bilirubin concentrations.

**Keywords:** Cholangioma; bilirubin; brain; icterus; histopathology

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## Introduction

Icterus is a clinical and pathological alteration arising from the occurrence of hemolytic, hepatic and/or hepatobiliary pathologies. It is defined as yellowish pigmentation of various parts of the body, such as mucous membranes and subcutaneous tissue. Bilirubin impregnation occurs as a result of above baseline serum levels.[1] It is a common clinical finding in a variety of diseases in veterinary medicine.[2]

Kernicterus is a condition characterized by the deposition and impregnation of bilirubin in brainstem neurons triggering brain lesions of varying intensity. It occurs secondary to hyperbilirubinemia and marked icterus.[2] The term kernicterus is only suitable for macroscopic diagnosis and is characterized by yellowish pigmentation in the brain. When referring to the associated clinical signs, the terms bilirubin encephalopathy or

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bilirubin-induced neurological dysfunction should be used.[3]

The main clinical and pathological findings of an adult cat with kernicterus due to hepatic and post-hepatic icterus are described in this report.

## Case description

A 14-year-old male shorthair mixed-breed cat with chronic kidney disease and hypertension presented with hyporexia, emaciation and prostration. Clinical examination revealed marked icterus, body condition score 3/5,[4] 5% of dehydration degree, nausea, weakness and abdominal pain.

The animal was hospitalized to perform a blood count and a biochemical profile. A complete blood count and biochemical profile revealed the following abnormalities, according to the reference intervals (RIs) for this species:[5] alkaline phosphatase (ALP) 544 IU/l (RI 0–93 IU/l); alanine aminotransferase (ALT) 1097 IU/l (RI 0–83 IU/l); serum bilirubin 7 mg/dl (RI 0.15–0.5 mg/dl); unconjugated bilirubin 2.05 mg/dl (RI 0–0.5 mg/dl) and conjugated bilirubin 4.44 mg/dl (RI 0–0.3 mg/dl). No changes were detected in hematocrit.

Abdominal ultrasound examination revealed hepatomegaly. The gall bladder was dilated, with a thick and irregular wall and microcysts in the mucosa, suggesting moderate cholecystitis. The common hepatic duct was dilated and in its final portion, close to the insertion in the duodenal papilla, there was marked wall thickening without lumen visualization, characterizing obstruction.

The animal remained hospitalized and developed anorexia. After 2 days, an esophageal feeding tube was placed. During hospitalization, the patient presented with sialorrhea, nausea, episodes of vomiting, lethargy, incoordination, dry feces, weight loss and worsening of icterus.

After 6 days, the blood count and biochemical profile were repeated. Results revealed mild anemia and regenerative neutrophil leukocytosis with left shift. There was a reduction in serum levels of hepatic enzymes (ALP 77 IU/l; ALT 817 IU/l). However, a serum bilirubin elevation (17.5 mg/dl) was detected (unconjugated bilirubin 6.73 mg/dl; conjugated bilirubin 10.78 mg/dl). As a result of these findings, the cat was referred to the Veterinary Hospital of the Federal University of Minas Gerais, for cholecystectomy surgery. Following surgery, the animal's condition worsened and it was transferred to the intensive care unit at the same institution. No histopathological examination was performed on the gall bladder.

The cat died 4 days later and was necropsied in the veterinary pathology sector at the same institution. External evaluation indicated the cat was in a poor nutritional state, with marked yellow pigmentation of the skin, as well as the ocular, oral and penile mucous membranes.

Grossly, the cortex of the cerebellar vermis, the lateral regions of the cerebellar hemispheres and the optic chiasma had markedly yellow areas, which extended into the parenchyma, predominantly in gray matter (Figures 1 and 2). The liver was diffusely reddish-orange and slightly enlarged, with bulged edges and with accentuated lobular pattern. The hepatic capsular surface was slightly irregular with some multifocal millimetric whitish areas that were also found in the parenchyma. The gall bladder was absent. A white mass, 2.0 cm in diameter, was found in the region of the common hepatic duct. It extended across the visceral surface of the left medial lobe (Figure 3).

The heart had left concentric hypertrophy. In the kidneys, the cortical surfaces of the subcapsular region were slightly irregular and the parenchyma was moderately firm. The medullary region was diffusely yellowish. On the pancreatic surface, there were some mildly elevated and firm yellowish areas, measuring 0.2 × 0.3 cm.

Samples of the brain, heart, liver, kidneys, lungs, intestines and pancreas were collected and fixed in neutral buffered 10% formaldehyde for 36 h. The samples were routinely processed, embedded in paraffin and sectioned at 3 μm for histological slide preparation. Subsequently, the slides were stained with hematoxylin and eosin. The pancreas was also stained with Congo red.[6] These slides were examined under a white light and polarized microscope, respectively.

Histologically, the brain lesions were restricted to the cerebellum and hippocampus. In the cerebellar gray matter, there was mild multifocal vacuolation of the neuron

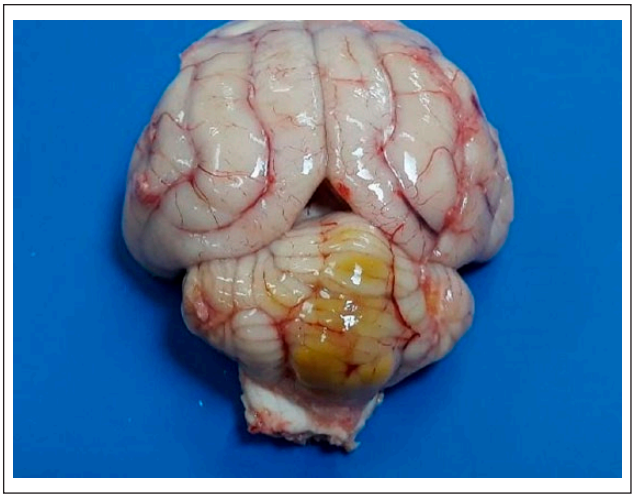

**Figure 1** Shorthair mixed-breed cat with kernicterus. Brain with marked yellowish pigmentation in the cortex of the cerebellar vermis and mild in the lateral regions of the cerebellar hemispheres

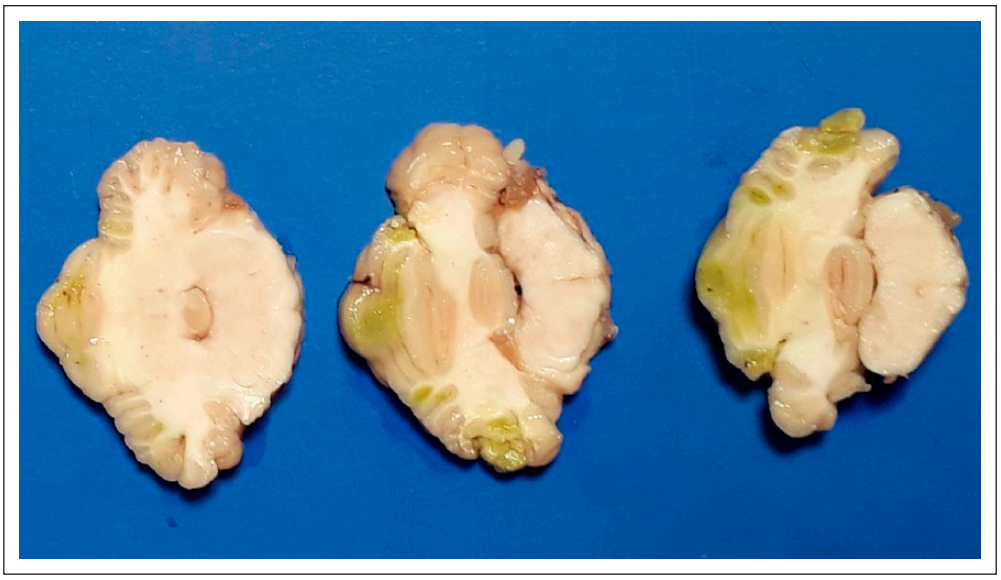

**Figure 2** Shorthair mixed-breed cat with kernicterus. Serial sections of cerebellum fixed in 10% buffered formalin. On the cut surface, the cerebellar vermis and the cerebellar hemispheres are yellow-to-greenish in appearance

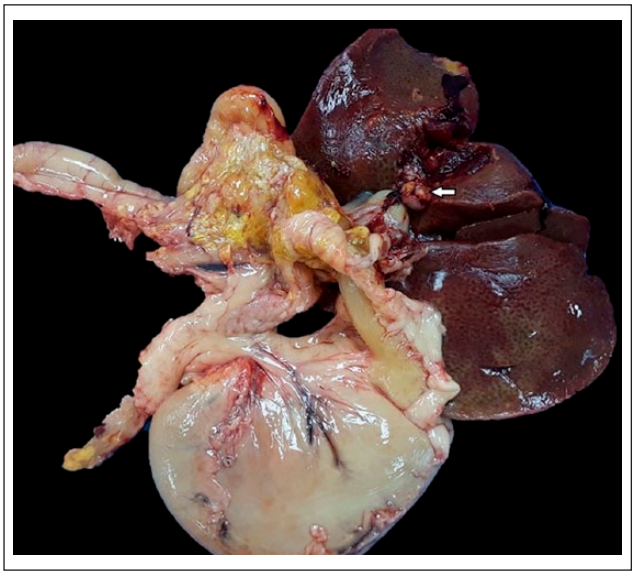

**Figure 3** Liver of a shorthair mixed-breed cat with kernicterus. Ventral view of the liver with absence of gall bladder and a nodule measuring 2.0 cm (arrow), diagnosed as cholangioma

bodies. Some neurons had eosinophilic cytoplasm and nuclear pyknosis or karyorrhexis, characterizing neuronal necrosis. The cytoplasm of some Purkinje layer neurons contained a moderate amount of granular and orange-to-brownish pigment (Figure 4). In the neuropil of the cerebellar white matter, there was moderate multifocal-to-coalescing vacuolation. In some vacuoles, there was marked axonal degeneration and a mild increase in the number of glial cells. In the hippocampus region, there were some neurons with karyorrhexis surrounded by microglial cells (neuronophagia).

The liver had random areas of multifocal-to-coalescing coagulative necrosis with minimal neutrophil infiltration, as well as biliary stasis. Moderate multifocal cholestasis was found in the cytoplasm of hepatocytes and most bile ducts. There was also moderate multifocal bile duct hyperplasia. In addition, a proliferation of well-differentiated tissue was found in the common hepatic duct. This proliferation was composed of tubular formations interspersed with dense connective tissue. A layer of poorly delimited cuboidal cells with eosinophilic cytoplasm was found lining the tubular lumen. Some tubules had two layers of cells. The nuclei were rounded, with loose chromatin, as well as a prominent nucleolus. Mild anisocytosis and anisokaryosis were found, as well as rare mitotic figures. These findings were consistent with cholangioma. Growth of the neoplasm resulted in the loss of adjacent hepatocytes and bile canaliculi.

The pancreas had changes in the endocrine and exocrine parenchyma. The pancreatic islets were replaced by eosinophilic and amorphous material. This lesion was diagnosed as amyloidosis. In the acinar part, there were multiple nodular hyperplasias. The capsule of the pancreas and the adjacent adipose tissue were replaced by an extensive fibrinous layer with cellular debris.

The kidneys had moderate multifocal membranous glomerulonephropathy with multifocal synechia and glomerulosclerosis. Renal tubule cells contained a moderate amount of brown granular pigment in the cytoplasm. The lumen of some tubules was filled with proteinaceous material. Moderate multifocal lymphoplasmacytic interstitial nephritis with fibrous tissue was

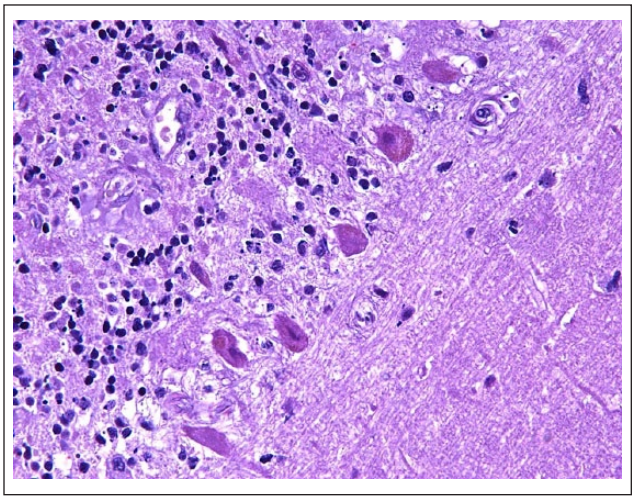

**Figure 4** Cerebellum of a shorthair mixed-breed cat. Cerebellar Purkinje neurons containing intracytoplasmic orange-to-brownish pigment are seen. Hematoxylin and eosin (× 400)

also found. In the heart, there was moderate hypertrophy of the muscle fibers.

## Discussion

The association of clinical, gross and histological changes favored a diagnosis of kernicterus in an adult cat caused by hepatic and post-hepatic icterus.

Kernicterus is a pathological condition triggered by an excess of free or unconjugated bilirubin. As it is lipophilic, it can cross the blood–brain barrier (BBB) and accumulate within neurons in specific areas of the brain.[7] Hyperbilirubinemia can occur when bilirubin production is elevated as a result of increased production (hemolysis), which exceeds albumin-binding capacity. It can also be caused by decreased conjugation with glucuronic acid due to hepatic lesions or ductal obstruction.[7,8] The icterus diagnosed in the cat of this report was classified as obstructive and hepatic. It is likely that the hepatic lesion contributed to the increased levels of unconjugated bilirubin.

The permeability of the BBB can be altered by hypoxia, inflammation, infection, drugs and acid–base imbalances.[2] Some studies have demonstrated that in prolonged hyperbilirubinemia, the unconjugated bilirubin could disrupt the integrity of the BBB. This also facilitates the entry of conjugated bilirubin into the brain parenchyma.[9] This may explain the bilirubin accumulation in the brain associated with obstructive icterus in the cat in this report.

The necrosis of hepatocytes in hepatic icterus may compromise the proper metabolism and excretion of harmful substances from the tissues and may facilitate failure to maintain the functions of the BBB.[10] Hepatic necrosis can be induced by obstructive icterus. This could impair sinusoidal endothelial cell function. The subsequent lesion from the obstructive icterus renders the liver susceptible to ischemia, resulting in hepatic necrosis.[11] In addition, the accumulation of intracellular bilirubin is toxic to cells, causing decreased protein synthesis, increased glycolysis, changes in mitochondrial oxidative phosphorylation and cell death.[12] The hepatic multifocal necrosis found in the animal of the present report might be associated with a lower capacity to conjugate bilirubin with glucuronic acid, facilitating the increase of unconjugated bilirubin in the circulation.

Areas of hepatic necrosis could also be induced by the marginalization of neutrophils in the sinusoids, which deliver reactive oxygen intermediates. These compounds can induce lesions in the sinusoid endothelial cells directly or induce the secretion of other inflammatory mediators, resulting in increased membrane permeability. In addition, neutrophils could degranulate and deliver proteases and oxidants, resulting in liver lesions.[11,13] In the present cat, some neutrophils were found in the areas of hepatic necrosis and may have contributed to the necrosis.

Unconjugated bilirubin, at low levels, acts to inhibit oxidative processes in cells. However, when unconjugated bilirubin increases, it impairs mitochondrial function, endoplasmic reticulum activity and the integrity of cell membranes, mainly in cells of the central nervous system. In cells, such as in neurons and astrocytes, bilirubin can cause degeneration and death.[14,15] In the animal of this report, unconjugated and conjugated bilirubin levels were well above the RIs, which possibly caused the neurological changes seen at presentation.

Kernicterus is considered a rare condition in veterinary medicine, with few scientific reports. However, its occurrence has been described in rats,[16] newborn rhesus monkeys (*Macaca mulatta*),[17] in a newborn cat,[18] in a 7-month-old cat,[19] in adult dogs[2,7] and in foals with neonatal isoerythrolysis.[20,21] The majority of the articles report that kernicterus was predominantly seen in newborn-to-young animals, in contrast to the animal in this report.

The concentric hypertrophy found in the heart may have been due to arterial hypertension. Hypertension was probably due to chronic renal disease with glomerulosclerosis. Alterations of degeneration and necrosis of renal tubular cells were probably due to the deposition of bilirubin pigment, causing bilirubinuric nephrosis.[22]

## Conclusions

Kernicterus is a neurological disorder that is rarely diagnosed in animals but with a high potential to trigger brain lesions of varying intensity. This report provides evidence that kernicterus can occur in adult cats, secondary to increased unconjugated and conjugated bilirubin concentrations. This cat's obstructed biliary

duct possibly caused hepatic necrosis with subsequent hepatic and post-hepatic icterus.

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