Peer Reviewed

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Increased Liver Enzyme Activity in a Dog

A 9-year-old neutered male Labrador retriever was referred for increased serum alanine aminotransferase (ALT) activity.

History. The increased ALT activity (4 times the upper limit of the reference interval) was noticed incidentally by the dog's primary care veterinarian 4 weeks earlier. A repeat serum biochemical profile obtained 2 weeks ago showed a similar elevation in ALT activity. The owner reported that the dog was not displaying any clinical signs of disease. Other than heartworm preventive, the dog was not receiving any medications and had no known exposure to toxins.

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ASK YOURSELF ...

Based on the history, physical examination, and laboratory and diagnostic imaging findings, which of the following would be your next step?

A. No further diagnostics at this time, but repeat a serum biochemical profile in 2 months
B. Measure pre- and postprandial serum bile acid concentrations
C. Test for leptospirosis, hyperadrenocorticism, and hypothyroidism
D. Perform a hepatic biopsy
E. Start treatment with hepatoprotectants and a commercial "hepatic support" diet

ALT = alanine aminotransferase

Physical Examination. The patient was judged to be overweight (body condition score of 7/9). Moderate dental calculus was noted on oral examination and bilaterial ceruminous discharge was noted on otic examination. No other abnormalities were found.

Laboratory Results. The results of a complete blood count and blood smear examination were unremarkable. A serum biochemical profile (**Table 1**) showed an ALT activity of 584 U/L (reference interval, 10–130 U/L). Urinalysis results were within normal limits.

Diagnostic Imaging. An abdominal ultrasound examination showed gastric distension but no other significant findings. No changes of the liver or biliary system were observed.

CONTINUES

Table 1. Serum Biochemical Profile Results

Variable	Result	Reference Interval
Glucose (mg/dL)	106	60–135
Cholesterol (mg/dL)	242	120–247
BUN (mg/dL)	13	5–29
Creatinine (mg/dL)	0.9	0.3–2
Magnesium (mg/dL)	1.8	1.7–2.1
Total calcium (mg/dL)	9.9	9.3–11.8
Phosphate (mg/dL)	3.7	2.9–6.2
Total protein (g/dL)	6.3	5.7–7.8
Albumin (g/dL)	2.9	2.4–3.6
Globulin (g/dL)	3.4	1.7–3.8
ALT (U/L)	584	10–130
ALP (U/L)	145	24–147
GGT (U/L)	9	0–25
Total bilirubin (mmol/L)	0.3	0–0.8
Sodium (mmol/L)	144	139–147
Potassium (mmol/L)	3.9	3.3–4.6
Chloride (mmol/L)	115	107–116

ALP = serum alkaline phosphatase; ALT = serum alanine aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyltransferase

CORRECT ANSWER: D. PERFORM A HEPATIC BIOPSY

ALT activity is a marker for hepatocellular damage **(Table 2)**. While serum alkaline phosphatase activity may be increased due to a number of extrahepatic conditions, increased serum ALT activity is considered to be a more specific marker for hepatobiliary disease.[1] This patient had ALT activity level greater than 4 times the upper limit of the reference interval, and this elevation persisted for more than 4 weeks. This finding suggested clinically important hepatobiliary disease and warranted further investigation.

Table 2. Causes of Increased Serum ALT Activities in Dogs

Primary Hepatopathies

- Inflammatory (acute hepatitis, chronic hepatitis, lobular dissecting hepatitis, copper hepatopathy)
- Neoplasia (primary, metastatic)
- Infectious (leptospirosis, infectious canine hepatitis, toxoplasmosis, *Heterobilharzia* infection)
- Trauma (contusions, herniation, torsion)
- Hyperplastic hepatic nodules

Secondary Hepatopathies

- Endocrine disease (diabetes mellitus, hyperadrenocorticism, adrenal hyperplasia)
- Inflammatory (enteritis, pancreatitis, peritonitis, systemic inflammatory response syndrome, sepsis)
- Hypoxia (anemia, thromboembolic disease, congestive heart failure, circulatory shock)
- Anaphylaxis
- Metabolic (storage diseases)

Xenobiotic-Related Causes

- Drug toxicity (barbiturates, carprofen, antimicrobials, azathioprine, glucocorticoids, griseofulvin, ketoconazole)
- Toxic (heavy metals, copper, carbon tetrachloride, petrochemicals, mycotoxins, blue-green algae, sago palm)

Extrahepatic Sources of ALT

- Severe muscle injury (uncommon)

ALT = alanine aminotransferase

Diagnostics. Because the liver has a considerable reserve capacity, patients with liver disease can have normal liver function test results.[2] The results of the dog's serum biochemical profile did not suggest hepatic insufficiency. Paired pre- and postprandial serum bile acid measurement is sensitive and specific for detecting hepatic insufficiency in dogs. However, in this case, serum bile acid measurement would not have aided in diagnosis or therapy selection.

Abdominal ultrasound is a useful imaging modality for evaluation of the hepatobiliary system. However, clinicians must recognize that patients may have clinically important hepatic parenchymal disease despite an apparently normal liver and biliary tract on abdominal ultrasonography.[3]

Extrahepatic Disease. Because of the liver's central role in metabolism and its unique dual blood supply, it is often affected by extrahepatic disease. Hepatopathies can be the primary disease process or can be secondary to extrahepatic disease, drugs, or toxins.[4] The diagnostic and therapeutic approach for patients with primary and secondary hepatopathies differs greatly. Based on the signalment, history, physical examination, and clinicopathologic findings, there was no evidence that this dog had extrahepatic disease or exposure to xenobiotics. Consequently, extensive testing for extrahepatic disease was not indicated.

Hepatic Biopsy. Collection of a hepatic biopsy was indicated due to the strong suspicion of a chronic primary hepatopathy. No evidence of a coagulopathy was found on a coagulation profile (including prothrombin time and activated partial thromboplastin time) or a buccal mucosal bleeding time.

Seven hepatic wedge biopsies were collected laparoscopically (**Figure 1**). Six of these were submitted for histopathology, and one specimen was immediately frozen. In addition, bile was submitted for aerobic and anaerobic culture. The frozen specimen was submitted for copper

quantification by flame atomic absorption spectrometry (Colorado State University Veterinary Diagnostic Laboratories; dlab.colostate.edu).

Diagnosis. Histopathologic evaluation of the liver biopsy specimens showed chronic periportal hepatitis with bridging fibrosis. Copper-staining showed accumulation of copper in hepatocytes (**Figure 2**). The hepatic copper concentration was 1651 ppm dry weight (reference interval, 120–400 ppm). The final diagnosis was copper-associated chronic hepatitis.

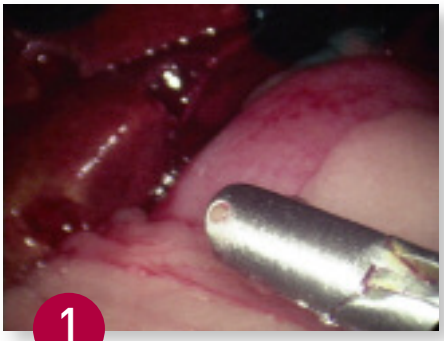
Treatment. The patient was switched to a commercial hepatic support diet with a vegetable protein source, restricted copper content, and increased zinc content.[5] Supportive treatment with ursodiol and SAMe was initiated. The patient's hepatic copper accumulation was treated with D-penicillamine.[6]

See Aids & Resources, back page, for references and suggested reading.

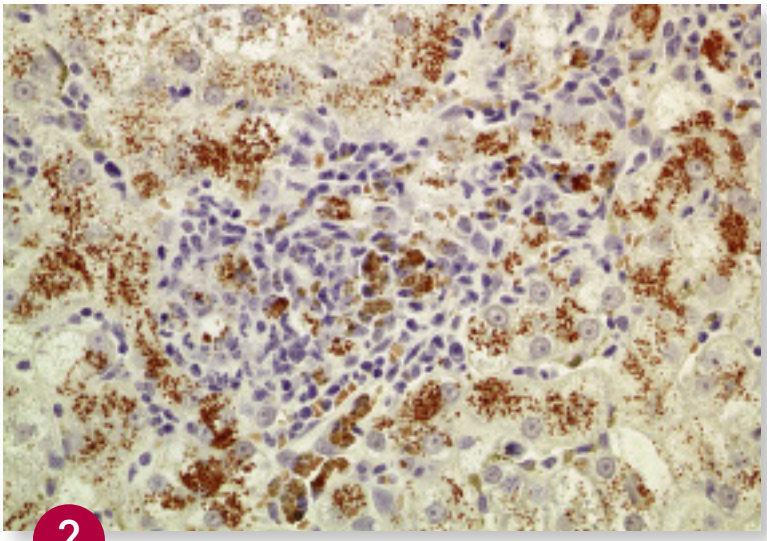
TAKE-HOME MESSAGES

- Depending on magnitude and duration, increases of serum ALT activity are clinically important and warrant further investigation.*
- Hepatic function tests can be normal in patients with early chronic hepatitis.
- Abdominal ultrasound examination can be unremarkable in patients with chronic hepatic parenchymal disease.
- Increases in serum hepatic enzyme activities can be from extrahepatic sources (eg, alkaline phosphatase can be of hepatic or bone origin) or due to primary or secondary hepatopathies.
- Biopsy is indicated in patients that are suspected of having chronic primary hepatopathy.

* In our opinion, further investigation is warranted when a single ALT activity determination is greater than 5 times the upper limit of the reference interval, or when multiple determinations demonstrate activity greater than 2 times the upper limit of the reference interval for more than 4 weeks.



1 Laparoscopic view of the liver; biopsy sites are visible on the margin of the liver



2 Copper-associated chronic hepatitis; this histopathologic section shows abundant copper granules in the cytoplasm of periportal hepatocytes and in some hepatocytes *Rhodamine stain; original magnification, 40x*

TX AT A GLANCE

- Treatment should be started as early as possible in the course of chronic hepatitis.
- Treatment should be guided by hepatic histopathology, hepatic copper quantification, and bile/liver culture.
- Chelating agents and reduced dietary copper intake are the main treatments for copper-associated chronic hepatitis.
- Hepatoprotectants have a place in the treatment of copper-associated chronic hepatitis.
- The use of corticosteroids and other antiinflammatory drugs in the treatment of copper-associated chronic hepatitis is controversial.
- Assessment of the patient's response to treatment is crucial.

SAMe = s-adenosylmethionine