

COPPER-ASSOCIATED LIVER DISEASES

Daniel K. Langlois, DVM, Diplomate ACVIM
Assistant Professor, Internal Medicine
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
Veterinary Medical Center, D-208
Michigan State University
East Lansing, MI 48824-1314

I. Background and Etiology

Copper is an essential micronutrient that is required for hundreds of enzymatic reactions throughout the body. However, excess tissue copper is pathologic and results in oxidative stress and inflammation. Pathologic hepatic copper accumulation, termed copper toxicosis or copper-associated hepatitis (CAH), was first described in Bedlington Terriers in 1979. The disease in this breed has been well-described, and identification of the causative mutation and selective breeding strategies have dramatically reduced disease prevalence. However, CAH is now recognized in additional breeds of dogs including West Highland White Terriers, Doberman Pinschers, and Dalmatians. And perhaps of most importance, CAH is now frequently identified in Labrador Retrievers, the most popular dog breed in the USA for over 25 years. While CAH in these breeds shares many similarities with disease in Bedlington terriers, the etiology is far more complex.

The breed predispositions and histologic pattern of copper accumulation suggest a genetic component. Mutations in the copper transport proteins ATP7A and ATP7B have been associated with CAH risk in Labrador Retrievers. However, mutations in these genes only account for approximately 12% of total heritability, and investigations of the genetic basis of disease in other breeds has not been successful. Furthermore, CAH is now being identified in many breeds and crosses not classically considered to be at-risk for CAH. These observations raise concerns for an environmental component.

In terms of environmental copper exposure, much focus has centered on the possible role of dietary copper excess. The original AAFCO nutrient requirements were not based on species-specific data. Additionally, the use of copper-oxide in mineral premixes was banned in 1997 due to poor bioavailability, and dog food companies transitioned to various other copper chelates. Notably, copper deficiency was not a problem at the time, and the bioavailability of the newer copper supplements were often 10 times greater than copper oxide. More recently, maximum copper levels have been removed in their entirety. These measures have likely led to increasing copper exposures in pet dogs. Two studies, including one from my institution, documented that the increased frequency of CAH started in the late 1990's shortly after the AAFCO requirements concerning copper supplementation went into effect. In the aggregate, these findings would suggest that dietary copper has indeed contributed to the high rate of CAH in recent years. It is likely that this dietary excess is exacerbating underlying genetic susceptibilities in some breeds.

II. Disease Recognition

The clinical signs of CAH are non-specific and typical of any dog with liver disease. Although CAH is considered a form of chronic hepatitis, many dogs have an acute exacerbation of clinical signs that appear similar to acute hepatitis or acute hepatic necrosis. Symptomatic dogs typically present for various gastrointestinal signs including anorexia, vomiting, and weight loss. Other clinical signs (icterus, abdominal distension) are variably present and dependent upon disease severity and chronicity.

Laboratory evaluation reveals increased liver enzyme activity in the majority of affected dogs, although some dogs with subclinical disease will have normal liver enzyme activity. In dogs with increased liver enzyme

activity, ALT is greater than ALP in nearly all cases. Despite commonplace thought that an increased ALT is only significant if 3-4 times above the reference interval, many affected dogs only have mild increases in ALT activity. As such, seemingly healthy dogs with persistently increased ALT activity, even if mild, warrant more detailed evaluation. One unique finding in some dogs with CAH is the presence of renal glucosuria or Fanconi syndrome. This should alert clinicians to the possibility of CAH as renal glucosuria is an uncommon finding in veterinary medicine.

III. Diagnostic Testing

The only way to definitively diagnose CAH remains liver biopsy with both histologic assessment and copper quantification. In general, clinically normal dogs with persistent unexplained increases in ALT activity (i.e. two documented increases 2 months apart) warrant hepatic biopsy. In symptomatic dogs with increased ALT activity, hepatic biopsy is often recommended earlier, especially in breeds predisposed to CAH. Both surgically and laparoscopically obtained specimens are suitable for diagnosis. Needle biopsies are limited by specimen size, but they can be used when other methods are not possible.

The classic histologic appearance of CAH is a chronic hepatitis which begins in the centrilobular regions of the lobule, and the inflammatory process can progress to involve all aspects of the lobule. Rhodanine or Rubeanic acid stained slides will reveal copper accumulation in these regions. Rhodanine scores are usually ≥ 3 (scale, 0-5) in affected dogs, although the degree of accumulation in subclinical cases may be less. Quantitative copper concentrations in normal dogs are usually less than 400 ppm (dry matter basis), and in dogs with CAH, concentrations often exceed 1000 ppm. Again, the magnitude of accumulation may be less in earlier cases.

IV. Disease Management

There are 2 primary aims of therapy:

- 1) reduce hepatic copper concentrations, and
- 2) control the clinical consequences of the copper excess.

There are 3 methods to reduce hepatic copper concentrations. Dietary copper restriction (Hill's I/d or Royal Canin Hepatic) can lower copper concentrations in some, but not all, affected dogs. It is also important to note that the amount of time required for a clinically relevant effect often exceeds 8 months. As such, this modality is best suited for patients with very mild disease or for maintenance therapy following more aggressive treatments. PO administration of zinc salts can prevent intestinal copper absorption, but again, the length of time for a positive effect is often delayed. Further, many dogs will vomit when receiving zinc salts, and this can preclude therapy in many affected dogs. Finally, hepatic copper can be removed in a more rapid manner using copper chelating drugs. D-penicillamine is widely considered to be the treatment of choice. The recommended dosage is 10-15 mg/kg PO BID. It is critical that this drug be given on an empty stomach or absorption will be blocked. To avoid GI upset associated with this drug, we will typically start at 50% of the target dose and concurrently use anti-emetics if needed. Most dogs require between 4 and 12 months of therapy.

As stated above, reductions in hepatic copper takes time, and clinically ill dogs will often require additional care during this period of time. A variety of supportive measures (antacids, anti-nausea medications, fluid therapy, etc) can be used as clinically indicated. In addition, all dogs with CAH should receive some form of antioxidant as copper directly induces oxidative stress. We typically use Denamarin®, but Vitamin E is also suitable for this purpose. Although strong evidence for these therapies is lacking, there is obvious rationale to their use. In dogs with more severe clinical illness and moderate to severe inflammation noted histologically, a tapering course of prednisolone (starting at approximately 0.5 mg/kg q 24h) often will result in improvement. Steroid therapy can usually be tapered over the following 1-2 months.

The overall outcome of dogs with CAH is variable. Those with advanced disease, including cirrhosis, acquired shunts, or ascites, have a guarded prognosis and usually do not survive beyond 3 months. Dogs diagnosed early in the disease course, such as clinically normal dogs with mild increases in ALT activity,

typically respond well to therapy and experience long-term survival. Some copper lowering therapy (usually diet or intermittent chelation) is usually needed in these dogs for life. Repeated hepatic biopsy is extremely helpful for assessing response to therapy in both the short- and long-term management of affected dogs.