

# COPPER-STORAGE LIVER DISEASE

## BASICS

### OVERVIEW

- Abnormal accumulation of copper in the liver, causing sudden (acute) inflammation of the liver (hepatitis) or long-term (chronic) hepatitis and eventually progressive damage and scarring of the liver (known as “cirrhosis”)
- Primary disease is thought to be the result of genetic-based abnormal copper metabolism
- Most of the following information is based on studies from affected Bedlington terriers

### GENETICS

- Autosomal recessive trait in Bedlington terriers due to the lack of a specific gene (COMMD1) coding for a protein involved in excretion of copper in the bile, which is produced by the liver
- The mode of inheritance in West Highland white terrier, Skye terrier and other breeds affected is unknown
- Dalmatians, Doberman pinschers and Labrador retrievers also have breed-related chronic hepatitis with copper accumulation (suspected to be a genetic disorder)
- Isolated dogs of other breeds with liver disease have been found to have elevated liver copper concentrations, but little evidence supports a genetic basis in these dogs
- Bedlington terrier—at one time, possibly as many as two-thirds of Bedlington terriers either were carriers of the gene or were affected by the disease; with recent genetic screening, the incidence is now much lower
- The prevalence in certain lines of West Highland white terrier appears to be high, but the incidence in all West Highland white terriers is low
- Reported 4% to 6% of Doberman pinschers may have chronic hepatitis
- The incidence in other breeds is unknown

### SIGNALMENT/DESCRIPTION of ANIMAL

- Dogs
- Rare, single isolated cases have been reported of abnormal copper accumulation in the liver of cats

### *Breed Predislection*

- Bedlington terriers, West Highland white terriers, Skye terriers, Doberman pinschers, Dalmatians and Labrador retrievers are reported to have increased liver copper concentrations

### *Mean Age and Range*

- Bedlington terrier—copper accumulates over time to a maximum level at about 6 years of age
- Dogs can be affected clinically at any age, though most present as middle-aged to older dogs having chronic hepatitis
- West Highland white terrier—maximum copper accumulation may be observed by 12 months of age, but clinical disease can occur at any time
- Skye terrier—all ages can be affected
- Doberman pinschers are reported to begin to develop hepatitis and copper accumulation at 1 to 3 years of age
- Labrador retrievers and Dalmatians are generally middle-aged when diagnosed with clinical disease

### *Predominant Sex*

- Doberman pinscher—females

### SIGNS/OBSERVED CHANGES in the ANIMAL

- Primary copper liver diseases (liver diseases are known as “hepatopathies”) generally fall in one of three categories: 1. subclinical disease (condition where the disease is present in the organ or body, but not detectable by abnormal signs or changes in the animal), 2. sudden (acute) disease (an uncommon finding) in which signs are observed most frequently in young dogs associated with acute death of liver tissue (known as “hepatic necrosis”), or 3. long-term (chronic) progressive disease in which signs are observed in middle-aged and older dogs with chronic inflammation of the liver (hepatitis) and damage and scarring of the liver (cirrhosis)
- Secondary copper liver diseases (hepatopathies) present with chronic progressive signs of liver disease due to chronic inflammation of the liver (hepatitis) or progressive damage and scarring of the liver (cirrhosis)
- Acute signs—sudden onset of sluggishness (lethargy), lack of appetite (anorexia), depression, and vomiting; weakness, and yellowish discoloration to skin and moist tissues (icterus or jaundice); pale moist tissues of the body (mucous membranes) due to low red blood cell count (anemia) and dark urine (due to the presence of bilirubin in the urine [bilirubinuria] and hemoglobin in the urine [hemoglobinuria]) in some dogs); many of these dogs have a rapid course and die despite intensive supportive treatment
- Chronic signs—history of waxing and waning sluggishness (lethargy), depression, lack of appetite (anorexia), and weight loss; vomiting, diarrhea, and excessive thirst (polydipsia) and excessive urination (polyuria) may be seen; later signs may include abdominal distention due to fluid build up in the abdomen (ascites), yellowish discoloration to skin and moist tissues (icterus or jaundice), spontaneous bleeding, black or tarry stools (melena), and nervous system signs due to the liver being unable to breakdown ammonia in the body (known as “hepatic encephalopathy”)

## CAUSES

- Primary—unknown in all but the Bedlington terrier; copper-storage liver disease in other breeds is suspected to be the result of abnormal liver copper metabolism or excretion defect
- Secondary—liver disease in which the flow of bile is slowed or stopped is known as “cholestatic liver disease;” the abnormal flow of bile results in secondary copper retention

## RISK FACTORS

- Primary—feeding high-copper diets, or stress factors that may precipitate acute disease

## TREATMENT

### HEALTH CARE

- Most dogs are treated as outpatients
- Inpatient evaluation and treatment are needed for dogs with signs of liver failure
- Treatment is determined by the type of disease: acute or chronic hepatitis or liver scarring/cirrhosis
- Animals in liver failure will require fluids and electrolytes

### ACTIVITY

- Normal

### DIET

- Low-copper diets should be fed to affected animals; however, almost all commercially available diets contain an excess of copper
- Balanced homemade diets avoiding copper-rich foods (such as organ meats) may be used
- Avoid mineral supplements containing copper
- Frequently, feeding a low-copper diet is not feasible, and commercial diets must be used
- Use of specific chemicals to tie up the copper in the system and to allow it to be removed from the body (known as “chelation therapy”) in conjunction with commercial diets has been successful in management of affected Bedlington terriers
- A high-quality, protein-sufficient, moderate-fat-containing diet should be fed to meet caloric needs; protein content should be reduced only when the patient exhibits protein intolerance (that is, has signs of liver-related central nervous system disease [hepatic encephalopathy])
- Water-soluble vitamins should be supplemented under the direction of your pet’s veterinarian

### SURGERY

- Liver biopsy may be needed to screen dogs for copper-storage liver disease and to monitor response to treatment
- Animals with liver failure are surgical and anesthetic risks

## MEDICATIONS

Medications presented in this section are intended to provide general information about possible treatment. The treatment for a particular condition may evolve as medical advances are made; therefore, the medications should not be considered as all inclusive.

- **d-Penicillamine** chelates copper (that is, ties up copper and allows it to be removed from the body) and promotes excretion of copper into the urine and is suspected to have other copper-protective effects; treatment should be initiated in affected dogs having abnormal hepatic copper concentrations
- **Trientine hydrochloride** is an alternative copper chelator that appears to be as effective as d-penicillamine
- Zinc reduces intestinal absorption of copper; may be beneficial in affected dogs in the early stages of copper-storage disease
- Use of chelators and zinc at the same time is not recommended and may decrease effectiveness of either drug
- d-alpha tocopherol (vitamin E) may protect the liver from damage caused by copper and is suggested as an additional therapy; vitamin E supplementation should be under the direction of your pet’s veterinarian
- Other antioxidants, such as s-adenosylmethionine (SAME) or silibin (milk thistle), may be beneficial; ask your pet’s veterinarian for recommendations

## FOLLOW-UP CARE

### PATIENT MONITORING

- Blood tests to monitor levels of liver enzymes every 4 to 6 months
- Monitor body weight
- Measure liver copper concentration within 1 year and thereafter as required by clinical findings
- When using zinc therapy, assess serum zinc concentration every 2 to 3 weeks, until concentration is stable and in desired range and then every 4 to 6 months

- Following therapy (6 months to 1 year) dog should be re-biopsied to monitor therapy; chelation therapy in affected dogs (Bedlington terriers, Doberman pinschers and Labrador retrievers) results in improvement of the hepatitis as seen on biopsy sections using a microscope

#### **PREVENTIONS AND AVOIDANCE**

- Breed only Bedlington terriers that do not carry the gene causing the disease; a liver registry is available for Bedlington terriers that are proven unaffected on the basis of liver copper concentration less than 400  $\mu$  g/g DW at 1 year of age or DNA gene evaluation

#### **POSSIBLE COMPLICATIONS**

- d-Penicillamine can cause lack of appetite (anorexia) and vomiting; d-penicillamine may, in rare cases, cause an autoimmune-like blistering (vesicular) disease of the areas where the skin meets the moist tissues of the body, such as the lips, (known as “mucocutaneous junctions”) that resolves on withdrawal of the drug
- Excess zinc concentrations can cause a breakdown of red blood cells (hemolytic anemia)

#### **EXPECTED COURSE AND PROGNOSIS**

- The prognosis is poor in acutely affected young dogs with severe liver failure or older dogs with progressive damage and scarring of the liver (cirrhosis)
- Young dogs with mild-to-moderate acute liver failure usually respond to chelation therapy; the prognosis is fair for these animals; the prognosis is good if the disease is detected before inflammatory changes are noted in the liver, and the dog is started on appropriate therapy

#### **KEY POINTS**

- All Bedlington terriers should be screened by using either DNA genetic markers or liver biopsy
- Other breeds should be monitored for abnormal liver enzymes or by liver biopsy
- Therapy is needed for life
- Affected animals should not be used for breeding

