



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 information on copper-storage liver disease is based on studies from affected Bedlington terriers; however, many other breed-associated liver disorders or diseases (known in general terms as “hepatopathies” [singular, hepatopathy]) having abnormal liver copper accumulation have been identified
- The liver is the largest gland in the body; it has many functions, including production of bile (a fluid substance involved in digestion of fats); bile ducts begin within the liver itself as tiny channels to transport bile—the ducts join together to form larger bile ducts and finally enter the extrahepatic or common bile duct, which empties into the upper small intestine; the system of bile ducts is known as the “biliary tree”

GENETICS

- Autosomal recessive trait in Bedlington terriers due to the *COMMD1* gene mutation involved in the excretion of copper in the bile, which is produced by the liver
- The mode of inheritance in West Highland white terriers, Skye terriers, and other breeds affected is unknown
- Dalmatians, Doberman pinschers and Labrador retrievers also have breed-related long-term (chronic) inflammation of the liver (known as “chronic hepatitis”) with abnormal copper accumulation (suspected to be genetic or familial [runs in certain families or lines of dogs] disorder)
- Isolated dogs of other breeds and mixed-breed dogs with liver disease have been found to have elevated liver copper concentrations, but little evidence supports a genetic basis in these dogs
- Bedlington terriers—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 terriers appears to be high, but the incidence in all West Highland white terriers is low
- Reported 4–6% of Doberman pinschers may have long-term inflammation of the liver (chronic hepatitis) and abnormal liver copper accumulations
- The incidence in other breeds is unknown

SIGNALMENT/DESCRIPTION OF PET

- Dog
- Cat—rare, isolated cases have been reported of abnormal copper accumulation in the liver

Breed Predispositions

- 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 terriers—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 long-term inflammation of the liver (chronic hepatitis)
- West Highland white terriers—maximum copper accumulation may be observed by 12 months of age, but clinical disease can occur at any time
- Skye terriers—all ages can be affected
- Doberman pinschers are reported to begin to develop inflammation of the liver (hepatitis) with increases in a liver enzyme (alanine aminotransferase or ALT) on bloodwork and copper accumulation at 1–3 years of age; clinical signs of liver disease often occur after 7 years of age
- Labrador retrievers and Dalmatians are generally middle-aged when diagnosed with long-term inflammation of the liver (chronic hepatitis)

Predominant Sex

- Doberman pinschers—females

SIGNS/OBSERVED CHANGES IN THE PET

- Primary copper-storage 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 pet), (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 liver copper accumulation can occur with long-term (chronic) progressive inflammation of the liver (hepatitis) or diseases in which the flow of bile is decreased or stopped (known as “cholestasis”)
- Acute signs—sudden onset of sluggishness (lethargy), lack of appetite (known as “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 buildup 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 copper-storage liver disease—proven in Bedlington terriers; copper-storage liver disease in other breeds (such as Dalmatians, Labrador retrievers, and West Highland white terriers) is suspected to be the result of abnormal liver copper metabolism or excretion defect
- Secondary liver copper accumulation—liver disease in which the flow of bile is slowed or stopped is known as “cholestatic liver disease” in some dogs; the abnormal flow of bile results in secondary copper retention

RISK FACTORS

- Primary—feeding high-copper diets, or stress factors that may precipitate sudden (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: sudden (acute) or long-term (chronic) inflammation of the liver (hepatitis) or liver scarring/cirrhosis
- Pets in liver failure will require fluids and electrolytes

- Treatment for nervous system signs due to the liver being unable to breakdown ammonia in the body (hepatic encephalopathy) or for a blood-clotting disorder (known as a “coagulopathy”) is necessary for pets with signs of these conditions

ACTIVITY

- Normal

DIET

- Low-copper diets should be fed to affected pets
- Therapeutic diets for pets with liver disease have the lowest copper content of commercially available diets and are suggested for feeding pets with copper-related liver disorders
- Balanced homemade diets avoiding copper-rich foods or ingredients (such as organ meats) may be used, but frequently are not feasible
- Avoid mineral supplements containing copper for any pet with liver disease
- 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 pet 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
- Pets 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; administer by mouth one hour before feeding
- Trientine hydrochloride is an alternative copper chelator that appears to be as effective as d-penicillamine; administer by mouth one hour before feeding
- Zinc reduces intestinal absorption of copper; may be beneficial in affected dogs in the early stages of copper-storage disease; ; administer by mouth one hour before feeding
- 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
- Ursodeoxycholic acid—recommended if the pet has long-term inflammation of the liver (chronic hepatitis)

Follow-Up Care

PATIENT MONITORING

- Blood tests to monitor levels of liver enzymes every 3–6 months
- Monitor body weight
- Measure liver copper concentration within 1 year of starting treatment
- When using zinc therapy, assess serum zinc concentration in the first 2–3 weeks and until concentration is stable and in desired range and then every 4–6 months

- Following therapy (6 months–1 year) dog should be rebiopsied 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; chelation therapy is the use of specific chemicals to tie up the copper in the system and to allow it to be removed from the body

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 µg/g DW at 1 year of age or gene testing

POSSIBLE COMPLICATIONS

- d-Penicillamine can cause lack of appetite (anorexia) and vomiting; d-penicillamine may, in rare cases, cause inflammation and accompanying dysfunction of glomeruli of the kidney (known as “glomerulonephritis”); inflammation in multiple joints (known as “polyarthritis”); an auto-immune-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 (known as “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 sudden (acute) liver failure usually respond to chelation therapy; the prognosis is fair for these pets; 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; chelation therapy is the use of specific chemicals to tie up the copper in the system and to allow it to be removed from the body
- The prognosis is good if the disease is detected before development of inflammation of the liver (hepatitis) in dogs given appropriate treatment

Key Points

- All Bedlington terriers should be screened using the COMMD1 gene test
- Do not breed affected Bedlington terriers or dogs carrying the abnormal gene
- Other breeds should be monitored for abnormal liver enzymes or copper liver accumulation by liver biopsy
- Therapy is needed for life
- Affected pets should not be used for breeding due to the potential genetic component of the disease in various breeds; genetics of other breeds have not been determined

Notes

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