

SYNDROMES OF ILL-HEALTH ASSOCIATED WITH COPPER

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In higher organisms, copper-containing enzymes are involved in the development and maintenance of the hemopoietic, cardiovascular, nervous, skeletal, reproductive and integumentary systems. In addition to these essential roles, copper is also involved in not yet fully understood non-enzymatic activities, such as angiogenesis, nerve myelination, and endorphin action. Although copper does not belong to the “heavy metals”, comprising arsenic, cadmium, lead and mercury, that are generally believed to pose the greatest risk of elements to animal health, it is interesting that in Israel, this mildly toxic metal actually causes more health problems than all the other 4 elements combined. This brief note will detail some important points regarding copper-associated syndromes that are seen in Israel, together with guidance on how one might prove the existence of possibly the most common such disorder, copper-associated hepatitis, recorded in dogs in other countries.

The most important syndromes are:

1. Copper toxicosis in sheep

Only one case of acute copper toxicosis in Israel has been reported, with mortality occurring in the act of dosing sheep with copper sulphate. Chronic copper toxicosis, although not infrequent in sheep in Israel, has never, to my knowledge, been reported in Israel in goats (very rarely abroad, with or without a hemolytic crisis), and never in cattle. Chronic toxicoses in sheep are seen worldwide, and as abroad, in Israel toxicoses are seen in certain breeds, nearly always in the Assaf breed (East-Friesian/Awassi crosses). Rarely toxicosis is seen in Merinos and in the unimproved Awassi breed. It is strange that although copper toxicosis in cattle is (uncommonly) seen abroad, it has not been recorded in Israel, despite the fact that beef cattle in Israel were once fed up to 10 kg of dried poultry litter daily (now <2 kg), and despite such litter being a major source of unintentionally added copper, the copper had no apparent ill effect. However, there is a report abroad of copper-induced liver damage in dairy cows that was “subclinical”, with no obvious manifestations seen.

Molybdenum plays a crucial role in the metabolic balance of copper in ruminants. The copper to molybdenum ratio in feed is of critical importance, and should be between 4 and 8 in the sheep diet. Increasing the copper to molybdenum ratio may result in copper accumulation and possibly chronic copper poisoning (especially in sheep), whereas decreasing the ratio may induce copper deficiency (especially in cattle). Dietary sulfate is reduced to sulfide in the rumen that can combine with molybdate to form thiomolybdates, such as tetrathiomolybdate, which binds strongly to copper before and after absorption, so effectively reducing copper levels. However, it should be realized that excess sulphur (usually as sulphates) in the feed or water may also induce polioencephalomalacia. Dietary

zinc may also lessen absorption of copper. Molybdenum is the most frequent interacting element in copper metabolism, and so determination of copper and molybdenum, as well as sulphur and zinc in tissues (liver and kidney) and feedstuffs, is recommended for diagnosis and for monitoring interactions.

The most common causes of copper toxicosis in Israel comprise excess copper in sheep concentrates or their total mixed ration (TMR), or getting concentrates formulated for other species, or cattle TMR, or dried poultry litter which may contain over 200 ppm dry weight of copper. Dried poultry litter intended for feeding to sheep should always be examined for copper content, and any dried poultry litter containing >25 ppm of copper should be fed with the utmost of caution to susceptible breeds.

2. Copper deficiency

Primary copper deficiency is due to inadequate dietary copper intake and occurs when animals eat plants from deficient soils or on soils in which copper is unavailable for physical or chemical reasons. Secondary copper deficiency is induced by a relative excess of other elements affecting copper metabolism, mainly molybdenum, sulphur (and sulphates), zinc, calcium, and iron. Selenium may also react with dietary copper, reducing its absorption from the gastro-intestinal tract. Systemic manifestations of copper deficiency are seen most often in cattle and comprise mainly diarrhea and poor weight gain, with varying degrees of pallor (gray or yellow) of hair around the eyes, swollen painful joints, and anemia. This syndrome has, to my knowledge, never been reported in ruminants in Israel, probably due to general soil copper sufficiency.

Nervous system manifestations in lambs and kids (“swayback”) are seen due to copper deficiency in their dams. At the critical period in late gestation when myelin is being laid down most rapidly, copper deficiency can cause a depression in the activity of COX, the copper-containing respiratory enzyme in the motor neurons, which leads to the inhibition of aerobic metabolism and phospholipid synthesis, and consequent inhibition of myelin formation. Demyelination has been associated with copper deficiency with swayback-like manifestations in sheep, goats, deer, and rarely in cats and man. The syndrome appears in two forms: 1) Neonatal swayback, manifested at birth, and usually fatal, lambs and kids showing only hindlimb paresis or paralysis; 2) The delayed form, enzootic ataxia, developing several weeks or months after birth. Swaying and uncoordinated movements of the hindquarters and staggering gait are the major manifestations of delayed swayback, but animals do not die from the syndrome. Swayback as a primary deficiency has been recorded only once in Israel, in sheep fed copper-deficient forage grown on the peat beds of the Hula valley. Secondary

copper deficiency was unknown in Israel, but in recent years has been found in about 5 flocks of sheep or goats annually, usually as the neonatal form, induced by supplementation of concentrates with molybdenum to prevent copper toxicosis. Instead of selectively adding this toxic element to feed of flocks susceptible to copper toxicosis, it has been the practice to illogically add molybdenum to all small ruminant feed, even in goats, in which copper toxicosis does not exist in Israel, and this has resulted in outbreaks of both neonatal and delayed swayback - copper deficiency - in both species. Veterinarians must be more selective and only prescribe molybdenum to be added to feed of specific sheep flocks.

3. Copper-associated chronic liver disease in dogs.

In contrast to the typical chronic exposure with acute manifestation of copper toxicosis in sheep, some species may show chronic exposure with chronic manifestations. Humans can suffer from an inherited copper storage disorder, wherein copper biliary excretion is reduced and copper accumulates in the liver and brain. A similar inherited autosomal recessive defect in the *COMMD1* gene in Bedlington terriers can cause chronic copper toxicosis in up to 60% of this breed in populations where no breeding to eradicate the *COMMD1* deletion has been practiced.

Primary hepatitis is the most common liver disease syndrome in dogs, estimated at about 0.5% of all clinical referrals, two-thirds comprising the chronic hepatitis form, one third of which is copper-associated and two-thirds is idiopathic. Dysfunctional copper excretion and subsequent copper-associated hepatitis (CAH) may be more prevalent than is assumed in other breeds of dogs, chiefly Labrador retrievers, Doberman pinchers, Dalmation terriers, West highland white terriers, Skye terriers, and less often other breeds; females often have a disproportionately high incidence. Copper accumulates in the liver over several years, and clinical manifestations of CAH develop gradually, mainly appearing in middle-aged or older dogs. Signs are usually non-specific and intermittent, with initially often a prolonged mild decrease in activity or appetite, followed by varying degrees of vomiting, anorexia, depression, lethargy and weight loss, and later polyuria/polydipsia, diarrhea and jaundice; this progression continues at a minimum of months and more often years. Dogs with elevated liver copper deposits are at a high risk of developing chronic hepatitis, and ultimately an irreversible cirrhosis, with often leads to death.

Diagnosis of liver damage is often initially expedited by serum analysis for increase in activity of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase and more specifically for CAH by analysis of biopsies for liver copper levels and liver histopathology. Copper is quantitated on a dry weight basis, and whereas levels in normal dogs are invariably <600 ppm, clinically-affected dogs often show >2000 ppm, but this "toxic" value varies greatly amongst the different breeds. A determinative diagnosis of CAH is very worthwhile as low copper diets and other therapeutic treatments are often efficacious in alleviating the clinical illness and avoiding progression of the syndrome. Feed-associated CAH is also possible, particularly in farm dogs that ingest copper-supplemented concentrates.

The Department of Toxicology has recently adopted a method to examine liver biopsies, in even very small samples (2 mg dry weight), from dogs with chronic manifestations such as in CAH, for the quantification of copper and other elements. In addition to elevations in copper concentrations in the liver, liver iron levels are very often elevated in CAH. Several other elements are analyzed in the same one analysis to ensure that the biopsy (if taken blind) was indeed only from liver tissue. As cholestasis, a sequel of most parenchymal liver diseases, can also increase liver copper levels, it is recommended to also perform histopathology from a liver biopsy, using a copper-specific stain for semi-quantitative appreciation of copper distribution. Increased liver copper subsequent to cholestasis is found in periportal areas whereas excess copper in CAH is invariably distributed centrilobularly. Other lesions typical of CAH will also be found.

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