

Swayback Disease in Ruminants

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Abstract

Swayback (enzootic ataxia), a disease caused by primary and secondary deficiency copper. This disease causes major economic losses; one hundred lambs are affected in single flock and up to 90 percent population of cattle can be affected in copper deficient areas. Congenital sway back, progressive spinal swayback and acute fatal swayback are three forms of disease. The diagnosis was based on sign and symptoms and presence gross cavitations and gelatinous lesions of the cerebral white matter. Myelin deficiency due to methylation cycle hindrance in spinal cord cells has been also seen. Most of histo-pathological lesions are due to improper functioning of copper dependent enzymes. Laboratory diagnosis can be done by determination of serum and liver copper levels. Disease can be minimized by manage copper in animal diets.

Keywords: Swayback, enzootic ataxia, copper, lamb, Copper.

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Introduction

Enzootic ataxia is a progressive neuropathy of young copper-deficient animals. It is also referred as sway back disease in England [1]. In initial stages of disease when signs are not pronounced it also referred as “lordosis” especially in human. This disease cause major economic losses in ruminant farming, as this diseases effect up to 50% of cattle population in Argentina and 90% of lamb flocks are affected in copper deficient areas [1, 2]. Primary and secondary deficiencies of copper lead to swayback. In primary deficiency the copper is deficient in diet of animal and in secondary deficiency copper is present in diet but not available for the absorption [1, 3]. The complexes of molybdenum and sulphur with copper made it unavailable at gut level [4, 5]. Risk factors for copper deficiency includes age, breed, specie, physiological state and body copper reserves of animals [3, 6 and 7]. Copper deficiency in diet also poses risk for swayback [8, 9]. Signs involve in-coordination and paralysis of hind limbs, blindness/deafness, anemia and falling prostrate [10]. Histopathology involves cerebellar lesions and loss of the Bergmann glial cells. These changes were seen consisted of patchy degeneration loss of the Purkinje both in the vermis and in the hemispheres. Damaged Pur-cells and reactive proliferating cells showed vacuolation, chromatolysis, and hyalinization of their cytoplasm [11]. Similar lesions were observed in a few neurons of the vestibular nucleus and reticular formation of the medulla oblongata. These lesions consisted of deficiency of stainable myelin, degeneration and loss of myelinated axons, and lack of inflammatory cells. The main

reason for most of neural lesion are improper functioning of copper dependent enzymes especially superoxide dismutase which is main player in body antioxidant protection system [12]. Diagnosis can be done by signs and symptoms and determining the copper serum and liver levels. Diseases status can be categorized as copper depletion, copper deficiency, body dysfunction and disease in copper deficient animals. Disease can be prevented and cured by oral administration of copper sulphate. Prevention is much better way as compared of treatment because prognosis is poor in those animals in which nervous system is involved.

Review of literature

Swayback is disease characterized by lameness in animals particularly in lambs and kids due to hind limb in-coordination [13]. This disease also referred as “enzootic ataxia” in Australia [14].

Etiology

Copper was declared dietary essential in 1924, and its deficiency leads to neural disease in small and large ruminants which is known as “Swayback or enzootic ataxia” [15].

Primary copper deficiency

It is referred as deficiency of copper in diet. The main reason for copper deficiency in diet is copper deficient soils, on which different types of forage are grown for animal consumption [16].

Secondary copper deficiency

It is referred to hampered absorption of copper in the gut due to various reasons which mainly

includes the interaction between copper, molybdenum and sulphur. These three elements bound each other to form copper thio-molybdate (CuMoS_4) which makes copper unavailable for absorption [17]. A study showed that sheep grazing on a pasture having moderate copper (12-20 mg copper/Kg DM) showed swayback disease in their newborn lambs due to high concentration of molybdenum and sulphur in that pasture [18].

Copper Transport and metabolism

Copper is an important mineral in the formation and functioning of the CNS [19, 20]. Copper is absorbed from the elementary canal of mammals and dispersed in all body organs and tissue via blood [21]. Blood is the only source of copper distribution in body [22]. Copper ion metabolism has been studied both in animals and man by various compartmental models [23]. Complexity of copper metabolism is indicated in a way that it not only works as a prosthetic group in various metallo-enzymes but also act as cofactor for at least thirty types of enzymes. Copper is associated mainly in ceruloplasmin and albumin [24] and excreted from gallbladder via bile [25]. Kramer [26] documented the review of copper transport and metabolism.

Scheme for copper metabolism in mammalians

Radio-copper⁶⁴ also used by several investigators to quantify copper turnover in trial animals. Dunn et al. [27] for example, made a 16-compartment model which was based on 3-d⁶⁴Cu turnover data. Intracellular transport mechanism of copper was demonstrated by Rosenzweig, 2001.

Copper Intracellular Transport

“Atx1” is Protein that binds copper in the 1 + oxidation state and delivered it to “P-type ATPase Ccc2” which is for translocation of copper across intracellular membranes. “CCS” is Copper chaperone and “Fet3” is multi copper oxidase localized at cell surface that do oxidation of Fe (II) to Fe (III).

Occurrence

Endemically copper is deficient worldwide in large animals and have high economic importance due to waste of fertile land having copper deficient pastures. In UK about 0.9% of cattle annually develop the signs of copper deficiency. Up to 90% of lamb flocks are affected from enzootic ataxia in severe copper deficient areas and most them die [28]. Copper

deficiency can be diagnosed by enzootic ataxia in pasture raised deer in New Zealand, where it is considered the most common trace mineral deficiency [29]. Cattle population up to 50% is effected by copper deficiency in the grazing lands of Benos Aires Province, Argentina [30]. Autumn is the more hazardous season in which the copper level in grasses is minimized [31].

Risk factors for copper deficiency

Risk factors for the decrease plasma copper levels can be divided into animal factors and dietary factors.

Animal factors

Age, breed, specie, physiological state and animal body reserves are the main animal risk factors to influence the copper deficiency. Primary copper deficiency is more common in young one than adults and signs are more pronounced in calves under two years of age [32]. The main reason for copper deficiency in young ones is the poor maternal status of copper and its poor secretion in the milk. Breed and species of animal also influence the copper status of animal. It is reported that Scottish blackface ewe absorbs copper with 50% less efficiency than Welsh Mountain ewe [33]. The copper deficiency is controlled by both maternal and own genes at time of birth. Similarly copper tolerance and requirement are significantly different in sheep and goats [34]. Copper requirements within the cattle breed also vary, for example Simmental needed more copper than Angus [35]. During gestation the maternal copper reserves from its liver shifted to fetal liver and if dams copper reserves are not enough then copper transfer to fetus is less efficient which leads to its deficiency in newly born animals.

Dietary actors

It includes, pasture composition, soil status copper, molybdenum and sulphur concentrations and dietary copper and iron levels. Absorption of copper in less fibrous diet is more than fibrous diet this explains why copper deficiency is problem of grazing animals. On the other hand only minor increase in molybdenum and sulphur levels in diet reduces the absorption of copper. The reason behind that is complexes formation among these three minerals. It is reported that when molybdenum concentrations in pasture increases from 2 mg/Kg DM to 4.6 mg/Kg DM it leads to decreases the serum and liver levels of copper in grazing red deer. Adequate copper in diet can be helpful to cope with its deficiency

however metabolism of copper can be interfered by dietary iron, which also hampers its

availability [36].

Table 1: Copper dependent enzymes

Enzyme	Function
Amine oxidase (Flavin containing)	Metabolism of neurotransmitters: nor-adrenaline, dopamine, serotonin and some dietary amines
Lysyl oxidase	Connective tissue synthesis- cross-linking of collagen and elastin
Amine oxidase (Cu containing)	Metabolism of amines- histamines, putrescine, cadaverine
Cytochrome C oxidase	Oxidative phosphorylation, electron transport in the mitochondrial membrane
Cu/Zn SOD	Antioxidant and free radical scavenger, oxidizes dangerous superoxides to safer hydrogen peroxide
Ceruloplasmin	Iron transport-oxidation of Fe ²⁺ to Fe ³⁺ , copper storage and transport, antioxidant and free radical Neutralizer
Ferroxidase	Iron transport and oxidation of Fe ²⁺ to Fe ³⁺ in intestinal cells to enable iron uptake
Dopamine beta-monoxygenase	Conversion of dopamine to nor-epinephrine
Tyrosinase	Melanin synthesis
Adenosylhomocysteinase	Regeneration of homocysteine from adenosylhomocysteine (S-Adenosyl-L-homocysteine) in the Methylation cycle.

Forms of disease

Improper synthesis of myelin sheath may occur even in the mid of gestation in fetal life. Extreme copper deficiencies lead to cerebrospinal swayback which is congenital form of disease. Lambs born are weak, unable to stand and fail to suckle. Cavitation and softening of white mater in cerebrum is also seen. Swayback when developed signs and symptoms after 3-6 weeks of age it is referred as progressive spinal sway back. A third form which is postnatal acute fatal swayback is also observed. In this form there is more delay of disease occurring but when occurs, it takes only 1-2 days to cause death of animal after recumbency due to swelling of cerebrum [37].

Pathogenesis and clinical findings

Deficiency of copper (hypocuprosis) hampered the function of copper metallo-enzymes, most of which are the part of antioxidant protection system which includes ceruloplasmin and copper/zinc superoxide dismutase (Cu/Zn SOD) [38]. Copper is the catalytic cofactor for these two enzymes. Cu/Zn SOD causes the dismutation of super peroxide anion, which neutralizes hydrogen peroxide and molecular oxygen. The role of ceruloplasmin is to facilitate the conversion of ferrous form of iron to ferric which makes it to transfer via transferrin to bone marrow for red blood cell formation. That's why there is hemosiderin deposition in copper deficient animals. DNA damage in cattle is also reported due to copper deficiency [39]. In enzootic ataxia/swayback the nervous tissue goes under damage due to copper deficiency. Due to hypocuprosis the activity of cytochrome c oxidase which is complex IV in electron transport chain is compromised which leads to degeneration of spinal cord [40]. Myelopathy may also cause by disturbances in the methylation cycle. In this cycle a copper

dependent enzyme, methionine synthase is involved which causes the transfer of methyl group. As outcome of this methylation cycle purines and myelin proteins are made. These products of methylation cycle are vital for the synthesis of myelin sheath (protective covering of spinal cord) is conceded which ultimately leads to myelopathy [41]. The myelopathy due to myelin deficiency affects the sulcomarginal-funiculi and dorso-lateral portion of spinal cord [42].

The abnormal changes in the cerebral cortex of swayback diseases animal includes Cavitation and vacuolation, a number of glioma, damaged cortical neurons and vacuolation of perivenous and perineuronal areas. Cell death and its reabsorption make empty spaces and leads to vacuolation and cavitation, due to this brain of swayback diseased animal gives spongy appearance. Cortical neurons are heavily damaged which is a main appearance of this disease. Another frequently found feature is astrogliosis in swayback and degenerative changes may also be observed in brain parenchyma, which are result of less oxygen supply due to cerebral edema. Deficiency of copper leads to inappropriate function of many enzymes such as ceruloplasmin, superoxide dismutase, tyrosinase, cytochrome C oxidase and dopamine. Due to this there is accumulation of free radicals peroxidation in brain parenchyma, which leads to demyelination. Reduced cytochrome oxidase activity may result in decreased phospholipid production and this makes cell and organelle integrity vulnerable. Adogwa indicated pathognomonic lesions involving chromatolysis, vacuolation and necrosis of brain stem and spinal cord motor neurons in swayback disease.

Laboratory diagnosis

Serum and liver copper levels are determined. Serum level are not reliable so liver sample are taken by biopsy. 50g of liver and kidney sample is enough for toxicological assays. For histology examination, mid-sagittally sectioned brain (half portion), cervical and lumbar spinal cord is submitted in the laboratory.

Table 2: Normal ranges

Species and Tissues	N.Level	Primary Cu Deficiency	Secondary Cu Deficiency
Cattle			
Blood Plasma(µg/mL)	1.26±31	< 0.5 and as low as 0.1-0.2	< 0.5 and as low as 0.2-0.3
Adult liver (µmol/Kg DM)	> 100	< 20 and as low as 4	< 10
Sheep			
Blood plasma (µg/mL)	0.7-1.3	0.1-0.2	0.4-0.7
Adult liver (µmol/Kg DM)	> 100(usually 350)	20	15-19

Phases of copper deficiency development

The development of copper deficiency can be divided into four phases:

- i. **Depletion:** Plasma copper concentrations remain constant (normal) but concentration at storage site decreases.
- ii. **Deficiency (Marginal):** Plasma copper concentrations start decreasing from normal.
- iii. **Dysfunction:** Loss in the enzymatic activity
- iv. **Disease:** Appearance of signs and symptoms (cellular damage).

Treatment and control

For the treatment of both primary and secondary copper deficiency, oral dose of 4g copper sulphate for calves (2-6 month) and 8-10 g (adult) is weekly given for 3-5 weeks. However response to treatment in advance stage is not encouraging. Copper supplementation in water is not appreciated because solution reacts with metals. 2-3mg/L of copper pallets of water can be recommended. Cattle on molasses based diets must have copper 10ppm in their diet. Parental injection of copper are also now used in field to overcome copper deficiency some examples are copper calcium edetate, copper methionate, copper glycinate and copper heptonate. Along these soluble glass preparations having cobalat, copper and selenium are also given in Scotland for treatment of the disease. Copper oxide particles and needle are also orally given which have slow releasing mechanism from fore stomach and abomasum.

Conclusion:

It is concluded that the prevention and cure of swayback through nutritional manipulation is one of best solution to cope this problem. Swayback is due to low level of Copper in blood and liver level. Cattle and sheep are most effective. Low level of copper in blood may be

Due to change the ratio of molybdenum in diet, high pH of intestine also reduces the absorption of copper, low grain diet also reduce copper absorption and breed/specie variation. Copper is integral part of many enzymes in body especially that neutralize free radicals and improper function of those enzyme lead to several neural disorders.

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