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Copper deficiency in dairy goats and kids[1]

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ABSTRACT.- Almeida V.M., Lima T.S., Silva-Filho G.B., Bom H.A.S.C., Fonseca S.M.C., Evêncio-Neto J., Souza F.A.L., Riet-Correa F. & Mendonça F.S. 2022. **Copper deficiency in dairy goats and kids.** *Pesquisa Veterinária Brasileira 42;e07162, 2022*. Laboratório de Diagnóstico Animal, Universidade Federal Rural de Pernambuco. Rua Dom Manoel de Medeiros s/n, Dois Irmãos, Recife, PE 52171-900, Brazil. E-mail: fabio.mendonca@ufrpe.br

The clinical, pathological and reproductive aspects of an outbreak of copper deficiency in dairy goats and kids from the semiarid region of Pernambuco, Brazil are described. Ten adult dairy goats with clinical signs of deficiency and four kids presenting enzootic ataxia born from copper deficient does were separated from the herd, and examined. In the dairy goats, the average serum concentration of copper was 6.1±2.8mmol/L and iron was 39.5±8.2mmol/L. In kids, the average serum concentration of copper was 3.8±0.9mmol/L and iron was 38.5±4.1mmol/L. Clinical signs in dairy goats consisted of pale mucous membranes, anemia, emaciation, diarrhea, achromotrichia, brittle hair and alopecia. The main reproductive alterations consisted of prolonged anestrus, embryonic resorption and high indices of retained placenta. The kids born from copper deficient dairy goats were weak, and presented neonatal or late ataxia until 70 days of life. Six dairy goats and four kids were necropsied. Most ovaries examined were small, firm and did not present viable follicles on their surface. Microscopically, there was reduction of viable follicles in addition to disorganization of follicular and stromal structures, with marked follicular atresia. Microscopically, changes in kids with enzootic ataxia consisted of neuronal chromatolysis and axonal degeneration, mainly in neurons of the spinal cord. In this study, the source of high iron was not identified, but it is known that outbreaks of copper deficiency can occur due to excess iron intake, mainly when adequate mineral supplementation is not provided for the goat herds.

INDEX TERMS: Mineral deficiency, trace elements, follicular atresia, anestrus, goats.

RESUMO.- [Deficiência de cobre em cabras leiteiras e cabritos.] Descrevem-se os aspectos clínicos, patológicos e reprodutivos de um surto de deficiência de cobre em cabras leiteiras e em cabritos da região semiárida de Pernambuco, Brasil. Dez cabras leiteiras adultas com sinais clínicos de deficiência de cobre e quatro cabritos com ataxia enzoótica nascidos dessas cabras foram separados do rebanho e examinados. Nas cabras leiteiras, a concentração média de cobre sérico foi de 6,1±2,8mmol/L e a concentração média de ferro sérico foi de 39,5±8,2mmol/L. Nos cabritos, a concentração média de cobre sérico foi de 3,8±0,9mmol/L e a concentração média de ferro sérico foi de 38,5±4,1mmol/L. Os sinais clínicos nas cabras consistiram em mucosas pálidas, anemia, diarreia, acromotriquia, pelos opacos e quebradiços e alopecia. As principais alterações reprodutivas consistiram em anestro prolongado, reabsorção embrionária e aumento da taxa de retenção de placenta. Os cabritos nascidos vivos dessas cabras nasceram fracos, com ataxia neonatal ou desenvolveram ataxia tardia em até 70 dias de vida. Seis cabras leiteiras e quatro cabritos foram necropsiados. Nas cabras, a maioria dos ovários examinados macroscopicamente eram pequenos, firmes e não apresentavam folículos viáveis em

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sua superfície. Microscopicamente, houve redução de folículos viáveis, além de desorganização das estruturas foliculares, com marcada atresia folicular. Macroscopicamente não foram observadas alterações nos cabritos com ataxia enzoótica. As lesões histológicas observadas nesses cabritos consistiram em cromatólise neuronal e degeneração axonal, principalmente em neurônios da medula espinhal. Neste estudo a fonte dos altos teores de ferro no soro não foi identificada, mas sabe-se que surtos de deficiência de cobre podem ocorrer devido ao excesso de ingestão de ferro, principalmente quando não é fornecida suplementação mineral adequada para os rebanhos caprinos.

TERMOS DE INDEXAÇÃO: Deficiência mineral, oligoelementos, atresia folicular, anestro, caprinos.

INTRODUCTION

Copper deficiency significantly affects ruminant livestock production in large areas of Brazil (Tokarnia et al. 2010) as well as other parts of the world (Gooneratne et al. 1989, Prohaska 2006, Suttle 2010, Gambling et al. 2011). The development of deficiency depends not only on the total concentration of copper in the diet, but on other factors that influence the absorption and availability of this mineral. In ruminants, secondary copper deficiency commonly occurs due to the reduced copper absorption, mainly caused by the excess intake of Mo, S, Ca (such as calcium carbonate), Zn, Fe, Mn, Co, Pb, and Cd. Dietary concentrations of these elements are of great importance because mineral content in pasture and forage varies with plant species, soil conditions, and fertilizer applications (Gooneratne et al. 1989).

Little importance has been attributed to iron as a cause of copper deficiency in ruminants raised in extensive or semi-intensive management systems (Humphries et al. 1983). On the other hand, the pioneering studies carried out by Carlos Tokarnia and Jürgen Döbereiner on ruminant diseases in Brazil from the 1940s to the 2000s showed that after phosphorus, copper represents the second most important mineral deficiency in several Brazilian states (Tokarnia et al. 1968, 1971, 1999, 2000). Interestingly, some studies have reported the occurrence of high levels of iron and low concentrations of serum and hepatic copper in cattle with two different conditions: "snoring disease" (Tokarnia & Döbereiner 1998) and sudden death syndrome (Riet-Correa et al. 1993, Marques et al. 2003). "Brisket disease" (Tokarnia et al. 1989), a disease whose low manganese and cobalt values are found in the liver of cattle, is suspected to be caused by elevated iron (Tokarnia et al. 1999). Cases of "snoring disease" (laryngeal neuropathy) and limb paralysis, both conditions associated with severe copper deficiency due to iron overload have been reported in goats (Almeida et al. 2017, Sousa et al. 2017).

In ruminants, a wide variation of clinical presentations are described in copper-deficient animals, which includes anemia, immunological, neurological, cardiovascular and integumentary abnormalities (Hill & Shannon 2019, Mendonça & Riet-Correa 2022). The reason for this lies in the basic function of copper in animal organisms. Copper is an essential trace mineral in a variety of metabolic functions, being essential for the activity of numerous enzymes, cofactors, and reactive proteins (Altarelli et al. 2019). Important examples of enzymes are ceruloplasmin, responsible for transporting copper and transferring iron to plasma; cytochrome C oxidase, which acts on the mitochondrial respiratory chain; dopamine-β-hydroxylase, which coordinates the conversion of dopamine into norepinephrine, and tyrosinase, which acts on melanin synthesis (Arredondo & Núñez 2005, Solano 2018).

Copper is also related to the proper functioning of the reproductive system and its deficiency leads to breeding impairment in varying degrees (Masters et al. 1983, Prohaska & Brokate 2002). In grazing ruminants, low fertility due to late or absent estrus, postpartum delay followed by anestrus, abortions and embryo resorption can be linked to copper deficiency (Wilkanowska & Kokoszyński 2015).

In northeastern Brazil, enzootic ataxia due to copper deficiency is reported frequently, but little attention has been given to reproductive alterations occurring in adult animals (Sousa et al. 2012, Silva et al. 2018, Fontes et al. 2019). In this region, recent studies indicate that low levels of copper and high levels of iron are constant throughout the dry (July to January) and rainy (February to June) seasons (Lima et al. 2021, Mendonça & Riet-Correa 2022). In the goat's farm where this study was carried out, outbreaks of copper deficiency occur frequently throughout the year, despite mineral supplementation, leading to variable copper-associated conditions such as anestrus, anemia, enzootic ataxia, laryngeal and limb paralysis, and sudden death. For this reason, we aimed to describe an outbreak of copper deficiency secondary to iron overload in dairy goats and neonatal kids, focusing on the clinical, pathological and reproductive alterations.

MATERIALS AND METHODS

This study was performed on a herd of 230 Toggenburg goats showing signs of severe copper deficiency in the semiarid region of Pernambuco, northeastern Brazil (7°59'21.3" S 35°31'08.6" W). The farm had 10 hectares and the herd was managed in a semi-intensive system, with access to native pasture and received in late afternoon shopped Buffel grass (*Cenchrus ciliaris*) and whole grain corn. The herd consisted of seven bucks, 112 does, 50 kids and 61 goats of different ages and sex. Fresh water came from a deep well and commercial mineral supplement was provided *ad libitum* and contained: Ca (218g/kg), P (71g/kg), S (20g/kg), Mg (20g/kg), K (28.2g/kg), Co (30mg/kg), Cu (400mg/kg), Cr (10mg/kg), Fe (2.500mg/kg), I (40mg/kg), Mn (1.350mg/kg), Mo (198mg/kg), Se (15mg/kg), Zn (1.700 mg/kg), F (710mg/kg), Vit A (135.000UI/kg), Vit D3 (68.000UI/kg), Vit. E (450UI/kg).

Information regarding the clinical history of the herd was obtained in interviews with the veterinarian responsible for the farm. Ten dairy goats and four kids presenting clinical signs of copper deficiency were chosen for a detailed examination. They were clinically examined for general condition, behavior, coordination, head posture, movement, appetite, mucosal color, rectal temperature, heart and respiratory rates, abdominal morphology, ruminant-reticular motility, and physical appearance of feces, urine and skin Radostits et al. (2007). From this, five severely affected dairy goats that did not give birth nor were pregnant were followed up during three months for evaluation of their estrus cycle (Almeida et al. 2021). Neurological examinations were performed as described by Riet-Correa et al. (2002). Blood samples were collected using the vacuum collection system in collection tubes for hemograms. To determine total plasma protein levels, blood samples were collected according to Lopes et al. (2007). To evaluate mineral serum concentrations, serum samples were analyzed using atomic absorption spectrometry.

The samples were weighed on an analytical balance, deposited in borosilicate tubes containing perchloric acid (4:1 v/v) and kept at rest for 12 hours. Therefore, the tubes were placed in a sample digester system (Microwave X-Plus Mars, CEM®) at a temperature of 150°C. At the end of digestion, 10ml of 0.1N hydrochloric acid was added and sent for analytical procedures. The elements Cu, Mo, Fe and Zn were accessed through mass spectrometry, using the Spectra-L200 device (Miles et al. 2001). Hematological values and concentrations of Cu, Fe, Mo and Zn in serum samples were analyzed according to mean and standard deviation.

Six does and four kids that died during the follow-up period of this study were necropsied and tissue fragments from heart, lungs, liver, spleen, kidneys, forestomachs, abomasum, small and large intestines, uterus, and ovaries were collected. From the CNS, fragments of the brain, brainstem, cerebellum, diencephalon and spinal cord were obtained. From the PNS, the collected fragments were the vagus nerve and cranial cervical ganglion. Samples were fixed in 10% buffered formalin and CNS and PNS samples were fixed in 20% buffered formalin. All samples were routinely processed and stained with hematoxylin-eosin (HE) and selected sections of ovaries were also stained with Masson's trichrome.

RESULTS

Reproductive disorders were first noticed during the yearling season where 15 kids presented neonatal enzootic ataxia and 17 developed late ataxia. These kids presented pallor of the mucous membranes, opaque and brittle hair, achromotrichia, lack of coordination, frequent falls, development of hindlimb paraparesis between 30-70 days of life and severe weight loss followed by spontaneous death. Kids with neonatal ataxia were born weak, had difficulty suckling and standing up due to limb paralysis.

Fifty does have been also mated with four males of proven fertility. On this occasion, 80% of the does (40/50) were not pregnant and 30 days after mating, the pregnancy rate was confirmed by ultrasonography at 90% (36/40). Before the end of the breeding season, a new evaluation was carried out and 70% of embryo resorption and low pregnancy results were observed (30%, 11/36). After this, 40 does were submitted to estrus synchronization, hormonal treatment and fixed-time artificial insemination (FTAI). Only 45% (18/40) were pregnant 30 days after insemination; and only 15% (6/40) were pregnant at 45 days after insemination, from which it can be inferred that 66% (12/18) had embryo resorption. From this lot, only 15% (6/40) delivered kids, but all does had retained placenta in the postpartum period.

Clinical signs were variable in severity, being moderate in two dairy goats examined and severe in eight. The mainly clinical picture observed consisted of pale mucous membranes, torpor, emaciation, and achromotrichia (Fig.1 and 2). In addition, five does presented alopecia, watery brown diarrhea and prolonged sternal recumbency. The does examined for the estrus cycle remained in constant anestrus during all the period of evaluation and according to the veterinarian of the farm, there were 23 dairy goats in permanent anestrus. Four kids, three presenting late and one presenting neonatal ataxia as described above were also found (Fig.3 and 4). Analyzing the history of the disease and considering all adult goats in the farm, the morbidity was 100% in the entire herd and mortality rates were 34.7% for the dairy goats and 60% for kids.

Red blood count and biochemical profile of dairy goats showed the average hematocrit and hemoglobin levels below the reference values (hypochromic microcytic anemia). An increase in the amount of Howell-Jolly bodies in erythrocytes was also noted. There was no change in total plasma protein levels (Table 1). Average serum copper and iron concentrations were 6.1±2.8mmol/L and 39.5±8.2mmol/L, respectively. In kids, the average serum copper concentration was 3.8±0.9mmol/L and serum iron concentration was 38.5±4.1mmol/L (Table 2).

The main gross lesions in the adult dairy goats were unspecific. Most ovaries examined were small, firm and did not present viable follicles on their surface (Fig.5). Three does presented severe pallor of mucous membranes, and focal dark red areas in the accessory and cranial lobes of the lung and in the ventral portion of the caudal lobe. In these animals, the mediastinal and mesenteric lymph nodes were swollen and enlarged. The rumen, reticulum and omasum contents were dry and two does presented watery abomasum content, and mild swollen of the mucosa folds. Four dairy goats presented mild edema of the small intestine mucosa, mainly in the jejunum and ileum. There were no significant gross changes in the uterus examined.

Microscopically, there was a severe decrease in viable ovarian follicles, disorganization of follicular and stromal structures, and secondary and tertiary follicles presented varying degrees of atresia, which was characterized by degeneration and necrosis of granulosa cells, and detached and floated granulosa cells into the follicular antrum. Frequently, there was moderate to severe replacement of the follicles by fibrous connective tissue (post-atresia repair) (Fig.6, 7 and 8). No microscopic lesions were observed in the uterus. In the mediastinal and mesenteric lymph nodes, there was a reduction in the number and size of lymphoid follicles with a small amount or absence of germinal centers, depletion of paracortical lymphocytes and prominent stromal cells. In the mucosa of abomasum there was mild to moderate infiltration of lymphocytes and plasma cells and mild edema of lamina propria and submucosa. This same pattern of lesions was observed in the small intestine. In two animals, there was

Table 1. Hematology findings in dairy goats exhibiting signs of copper deficiency

Variable	Dairy goats	Kids	Reference values
RBC x 10^6/µL	12.0 ± 3.5	11.2 ± 1.8	8.0 - 18.0 (x 10^6/µL)
Htc, 1%	18.7 ± 5.7	17.4 ± 2.1	22.0 - 38.0 (%)
Hb, g/dL	5.8 ± 3.4	5.1 ± 2.7	8.0 -12.0 (g/dL)
MCHC, (%)	28.3 ± 0.8	28.1 ± 1.4	30.0 - 36.0 (%)
MCV, fl	14.8 ± 3.7	14.3 ± 1.7	16.0 - 25.0 (fl)
MCH, pg	5.9 ± 2.0	5.3 ± 0.9	5.2 - 8.0 (pg)

Hb = hemoglobin, Htc = hematocrit, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MHC = mean corpuscular hemoglobin, RBC = red blood cell.

Table 2. Serum concentrations (mmol/L) of Copper and Iron in dairy goats exhibiting signs of copper deficiency

Variable	Dairy goats	Kids	Reference values[a]
Copper	6.1± 2.8	3.8 ± 0.9	9.4-23.6
Iron	39.5 ± 8.2	38.5 ± 4.1	34.6-37.4

[a] Suttle & Peter (1985).

Fig.1-4. Copper deficiency in dairy goats and kids. (**1** and **2**) Herd of dairy goats exhibiting different levels of achromotrichia. (**2**) From the left to the right, a normal dairy goat with dark brown fur, and moderate to severe cases of achromotrichia with dairy goats presenting fur discoloration reaching to white. (**3**) Kid with hindlimb paraparesis in a case of late ataxia. (**4**) Permanent recumbency due to inability to stand up in a case of neonatal ataxia.

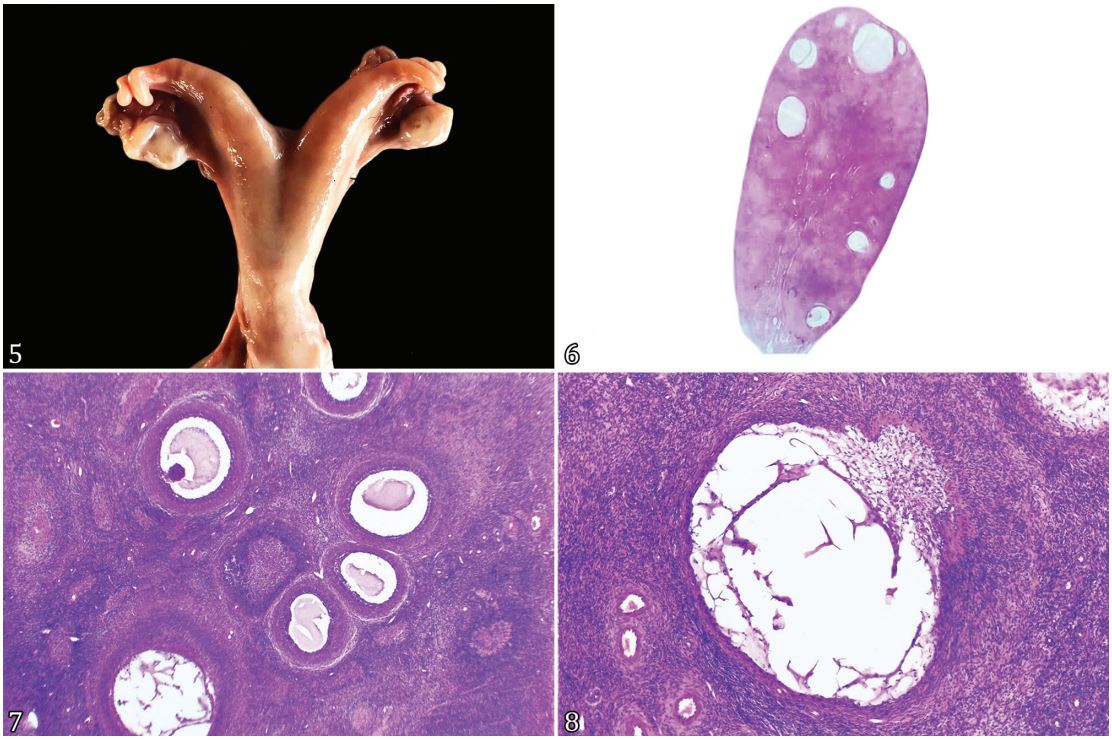

Fig.5-8. Reproductive changes in copper-deficient dairy goats. (**5**) Ovaries are reduced in size, firm, pale to white and without viable mature follicles on the surface. (**6**) Subgross of ovary with few ovarian follicles in the cortex, in which most of them do not have oocites and corona radiata. (**7**) Ovarian follicles in varying degrees of atresia with remarkable replacement of the granulosa cells layer by fibrous connective tissue. HE, obj.4x. (**8**) Note degeneration and necrosis of the granulosa cells that floated inside the follicular antrum and replacement of granulosa cells by connective tissue. HE, obj.10x.

mild lymphoplasmacytic enteritis. In the lungs, the lesions consisted of hyperemia and interstitial edema with infiltration of mononuclear polymorphonuclear leukocytes.

No significant gross lesions were observed in kids presenting neonatal or late enzootic ataxia. Histological findings were similar and consisted of degeneration and loss of Purkinje cells in the cerebellum. Additionally, Purkinje cells, and neurons from medulla oblongata, and ganglia presented chromatolysis and cytoplasmic hyalinization (Fig.9). In the gray matter of the cervical, thoracic and lumbar portions of the spinal cord, motor neurons showed cytoplasm and diffuse chromatolysis with marginalization of the nuclei. This lesion was observed mainly in the ventral funiculus. In addition, in the white matter there was severe axonal with myelin sheath expansion and the presence of vacuoles, usually in chains and containing axonal debris or macrophages (Fig.10).

DISCUSSION

The outbreak of copper deficiency reported here in the dairy goats was characterized by different severity levels of apathy, weight loss, emaciation, achromotrichia, alopecia, severe anemia, anestrus, embryo resorption, retained placenta in the postpartum period, and prolonged recumbency. Enzootic ataxia in kids was also a frequent finding. Most reports of copper deficiency in Brazil have been describing late ataxia in ruminants (Mendonça & Riet-Correa 2022), but there are only few reports describing severe pictures of copper deficiency in adult goats as we are describing here (Almeida et al. 2017, Sousa et al. 2017).

To our knowledge, there are no reports highlighting the reproductive pathology in cases of copper deficiency in dairy goats. Nevertheless, in buffalo-cows an association between ovarian inactivity and copper deficiency was described. In these cases, buffalo-cows also presented small and firm ovaries without viable follicles on their surface. Affected animals exhibited low serum levels of progesterone during the luteal phase of the estrous cycle, anemia and a reduction of several enzymes, which has been implicated in oxidative stress with consequent cessation of ovarian activity (Ahmed et al. 2009). It is possible that the reproductive changes mentioned above result from the low interaction of copper with GnRH receptors, which interferes with the release of LH through a calcium-dependent mechanism (Michaluk & Kochman 2007). Unfortunately, levels of GnRH, FSH or LH were not possible to perform in this study.

Anemia in ruminants due to copper deficiency is seen only after extreme and prolonged deprivation of this mineral (Suttle 2012). Copper is a cofactor of ceruloplasmin and cytochrome oxidase and deficiency of the activity of these enzymes triggers anemia due to dysfunction in iron transport to erythrocytes and hemoglobin synthesis. As the bone marrow does not suffer normoblastic hyperplasia and the erythrocyte, maturation becomes defective. Probably this is the main mechanism triggering the anemia observed in the dairy goats reported here (Suttle 2010, Underwood & Suttle2010).

The clinical picture and pathology of copper deficiency in ruminants can be variable according to several factors such as the species and minerals involved, and the duration of depletion. For example, iron-induced hypocupremia in cattle may be asymptomatic, whereas hypocupremia of equal severity induced by molybdenum is remarkable (Phillippo et al. 1987). Previously we described a clinical picture in hypocupremic adult goats mainly consisting of ataxia, laryngeal paralysis, severe achromotrichia (Sousa et al. 2017), and monoparesis of the hindlimb (Almeida et al. 2017). Other clinical signs included apathy, emaciation, pallor of mucous membranes, mucous nasal secretion, dyspnea, diffuse alopecia and torpor (Almeida et al. 2017, Sousa et al. 2017). In the herds investigated, we did not observe anestrum, embryo resorption, and retained placenta in the postpartum period. These alterations could be also present in dairy goats in these herds, but were not diagnosed. On another hand, the clinical and pathological picture observed in kids was similar to those previously reported in the literature. However, the morbidity and mortality rates were higher than that observed in other reports (Santos et al. 2006, Radostits et al. 2007, Guedes et al. 2007, Sousa et al. 2012).

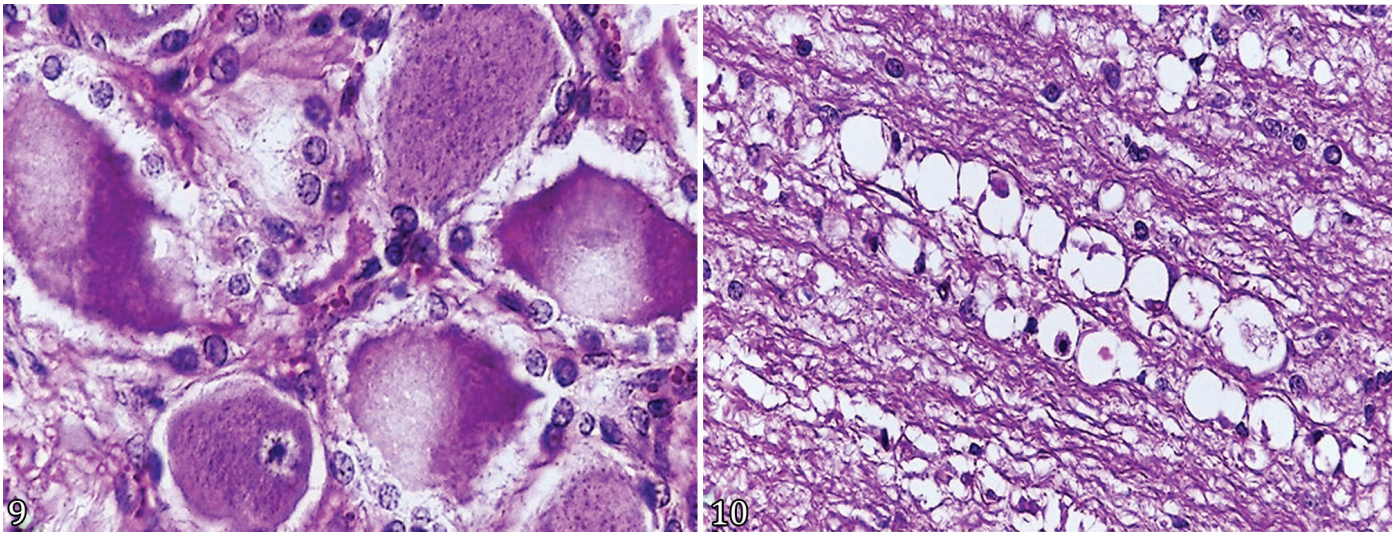

Fig.9-10. Late enzootic ataxia in goat kids. (**9**) Photomicrograph of cervical ganglion neurons with gliosis and neuronal central chromatolysis. HE, obj.40x. (**10**) Photomicrograph of spinal cord white matter with axons presenting axonal degeneration, mainly characterized by the formation of vacuoles in chains and containing axonal debris and macrophages. HE, obj.40x.

There was no information regarding the quality of the pasture and soil of the farm to accurately estimate the origin of the mineral deficiency in this outbreak of copper deficiency. The disease was observed throughout the year; for this reason, factors related to inadequate supplementation as well as soil and pasture high levels of chelating minerals (possibly iron) could be the main factors that triggered the occurrence of the deficiency. Normal values of copper and iron for goats' ranges from 9.4-23.6mmol/L and 34.6-37.4mmol/L, respectively. For this reason, the concentrations of serum copper (6.1±2.8mmol/L) and iron (39.5±8.2mmol/L) from goats in this study characterizes a moderate to severe copper deficiency associated with high serum levels of iron. The copper deficiency was also remarkable in the kids (copper was 3.8±0.9mmol/L and iron was 38.5±4.1mmol/L).

In a previous study, we reported an outbreak of copper deficiency associated with high serum and liver iron concentrations in a different farm in the same region (Sousa et al. 2017). In this study, we also reported high levels of iron in the soil and forage consumed by goats presenting severe copper deficiency (Sousa et al. 2017). In the northeastern semiarid region of Brazil, many sheep and goat herds have marginal concentrations of serum and liver copper. In part, this is due to the high content of iron in pastures or water or the ingestion of mineral supplements containing high concentrations of this mineral. Soil intake may also be responsible for the high iron intake, which suggests that low copper concentrations in the liver of sheep and goats in northeastern Brazil are perhaps, at least partially, secondary to high iron intake (Mendonça & Riet-Correia 2022). In this study, high serum concentrations of iron suggest that copper deficiency may be due to the ingestion of iron in excess. However, the source of high iron was not identified, and the participation of other chelating oligoelements in the pathogenesis of this outbreak cannot be ruled out.

The clinical signs, gross and microscopic lesions in dairy goats and kids reported here must be considered for the diagnosis of copper deficiency. To treat this severe deficiency, adult goats must receive subcutaneous applications of copper, at a dose of 0.1ml/kg of live weight (Sousa et al. 2017) and sources containing high levels of chelating oligoelements (water, soil or pasture) must be corrected. Mineral supplementation attending goat's requirements must be given daily *ad libitum* during and after the treatment.

CONCLUSION

The main reproductive alterations associated with severe copper deficiency in goats are prolonged anestrus, embryonic resorption and high indices of retained placenta. These alterations are related to reduction of viable follicles in addition to disorganization of follicular and stromal structures, with marked follicular atresia.

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