BJVP
Brazilian Journal of Veterinary Pathology
ISSN 1983-0246

Case Report

Renal encephalopathy due to acute renal failure in a goat

Fábio B. Rosa[1], Mara I. B. Rubin[1], Paula V. Leal[2], Tessie B. Martins[2], Danilo C. Gomes[2], Marcelo A. Araújo[3], Ricardo A. A. Lemos[2], Claudio S. L. Barros[2*]

[1]Programa de Pós-Graduação em Medicina Veterinária, Centro de Ciências Rurais (CCR), Universidade Federal de Santa Maria (UFSM), Camobi, Santa Maria, RS 97105-900, Brazil.
[2]Laboratório de Anatomia Patológica - Faculdade de Medicina Veterinária e Zootecnia (FAMEZ), Universidade Federal de Mato Grosso do Sul (UFMS), Av. Senador Filinto Müller 2443, Campo Grande, MS 79074-460, Brazil.
[3]Setor de Clínica Médica e Cirúrgica de Grandes Animais (FAMEZ/UFSM).
[*] **Corresponding Author:** Universidade Federal de Mato Grosso do Sul (UFMS), Av. Senador Filinto Müller 2443, Campo Grande, MS 79074-460, Brazil. E-mail: claudioslbarros@uol.com.br

Submitted August 29th 2015, Accepted September 8th 2015

Abstract

Renal encephalopathy was diagnosed in a 7-month-old male goat with a history of diarrhea and dehydration due to *Eimeria* sp. infection. The goat was treated with sulfadiazine before developing central nervous system (CNS) signs characterized by severe anorexia, salivation, tremors, inability to stand and depression. Biochemical parameters revealed high levels of blood urea nitrogen (BUN) and creatinine, 263.6 mg/dL and 2.9 mg/dL respectively. No gross pathological changes were observed at necropsy. Histopathological examination of the brain revealed large irregular empty spaces (status spongiosus) in the white matter of the brainstem, cerebellum, thalamus, basal nuclei and in the interface of white and grey matter in the cerebrum. There was severe multifocal renal tubular necrosis characterized by abundant deposits of basophilic granular material, frequently forming crystals that replaced the lost tubular epithelial cells and filled the lumina. The clinical-pathologic findings support to a diagnosis of encephalopathy due to acute renal failure.

Key words: diseases of goats, renal encephalopathy, status spongiosus, acute renal failure, sulfadiazine.

Introduction

In humans, an encephalopathy subsequent to the development of severe renal failure is well recognized, but in the veterinary literature very few cases have been described (4, 7). Renal encephalopathy has been observed in cattle, goats, dogs, horses and woodchucks (1, 2, 5, 11, 14, 16). Although this is a diffuse encephalopathy, CNS signs are chiefly referable to the prosencephalon including various behavioral changes – star gazing, inappropriate vocalization, aggression, agitation, propulsive walking or circling. Other clinical signs include lethargy, head pressing, ataxia, blindness, collapse, and coma. Classically these signs wax and wane from day to day, and in many cases can be precipitated by feeding the animal with a high-protein diet (13). The nervous dysfunction is associated with extensive and well-developed vacuolation of myelin sheaths, (spongy degeneration or status spongiosus) which tends to be most intense at the interface of the cerebral cortex and adjacent white matter, and around the deep cerebellar nuclei. Spongy degeneration is found also in the internal capsule, thalamus, hypothalamus, cerebellar medulla and peduncles, and pons and medulla oblongata (9, 13, 14).

Numerous toxic substances used as therapeutic agents can cause acute tubular lesion in domestic species resulting in acute renal failure. Some of these agents are no longer important as nephrotoxins, but even with the new formulations more soluble and less toxic, sulfonamides still are important nephrotoxins (12). The toxicity of these nephrotoxic agents is exacerbated by several systemic states, such as dehydration or shock, which concomitantly impair renal function. Sulfonamides are a well-known cause of severe nephropathy when administrated in

 All rights reserved 2007.

excessive doses and especially if the treated animal is dehydrated (8). This substance leads to crystalline nephropathy characterized by tubular necrosis and deposits of crystals in the tubular lumen (8, 10, 12, 15). In the past the toxicity was much more common, when only less-soluble forms of the drug were available, e.g., sulfapyridine, sulfathiazole, and sulfadiazine. Currently, due to new short-acting sulfonamides with greater solubility, sulfonamide toxicosis is a rare event (8).

Renal encephalopathy has rarely been reported in small ruminants. This study describes a case of renal encephalopathy with status spongiosus associated with severe acute renal failure in a goat.

Case report

A 7-month-old male goat was part of a group of 30 goats used in a metabolic experimental study at the Veterinary Hospital of FAMEZ/UFMS in the state of Mato Grosso do Sul, Brazil. The goat initially developed diarrhea and dehydration for two days. Due to a high count of *Eimeria* sp. oocysts per gram of feces the goat was treated with intramuscular sulfadiazine 20 mg/kg daily for five days. During these five days the goat presented CNS signs characterized by severe salivation, tremors, inability to stand and apathy. BUN was 263.6 mg/dL (reference value 21.04 - 42.8 mg/dL) (6) and serum creatinine was 2.9 mg/dL (reference value 1.0 - 1.8 mg/dL) (6). Albumin, aspartate aminotransferase and gamma glutamyltransferase seric values were within normal reference values. At postmortem examination no gross lesions were observed. Tissues from multiple organs, including the brain, heart, liver, lung, spleen, kidney, and intestine, were sampled and fixed in buffered 10% formalin. Paraffin sections, 3 µm thick, were prepared and processed routinely and stained with hematoxylin and eosin (H&E) for histopathologic examination. Histopathological findings in the brain consisted of large empty intramyelinic spaces in the white matter in the brain stem, cerebellum (Fig. 1), thalamus, basal nuclei (Fig. 2) and in the interface of the cortical grey matter and subcortical white matter of the cerebrum. The kidney had severe tubular necrosis characterized by abundant deposits of basophilic granular material that replaced the lost tubular epithelial cells and filled the tubular lumina (Fig. 3 and 4). Frequently this material formed basophilic to amphophilic crystals. There were no significant microscopic changes in other organ systems.

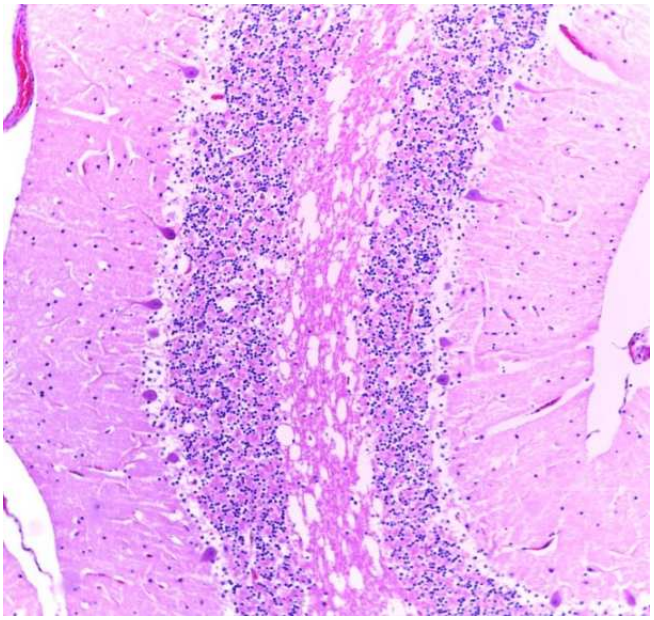


Figure 1. Histology of the brain of a goat dead from renal encephalopathy. Cerebellar medulla. Marked spongy degeneration of the white matter. HE, obj.20x.

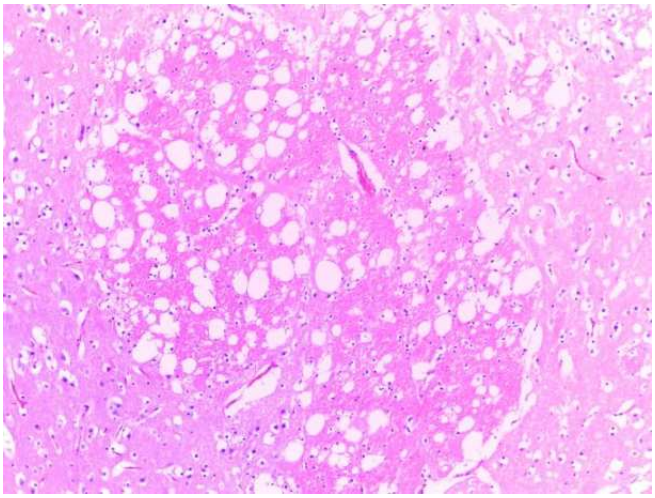


Figure 2. Histology of the brain of a goat dead from renal encephalopathy. Basal nuclei and internal capsule. Severe spongy degeneration in the white matter of the internal capsule. HE, obj.40x.

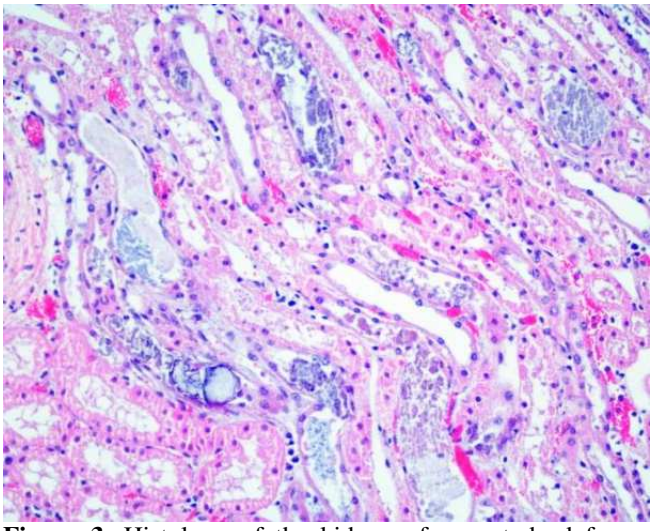


Figure 3. Histology of the kidney of a goat dead from renal encephalopathy. Severe multifocal tubular necrosis with intratubular crystals. HE, obj.20x.

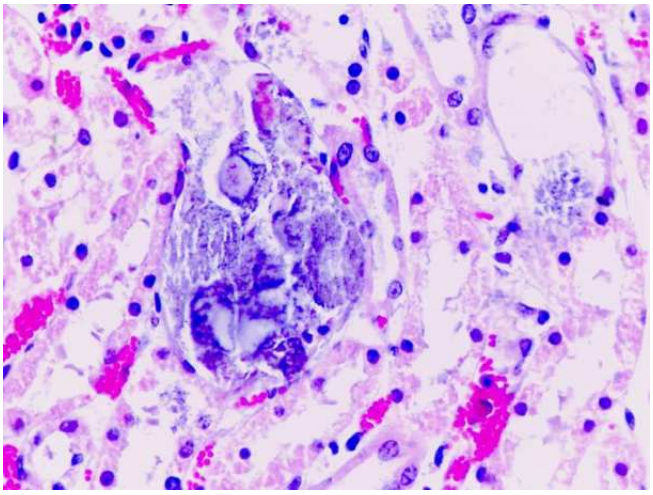


Figure 4. Histology of the kidney of a goat dead from renal encephalopathy. Replacement of lost epithelial tubular cells by crystals that obliterate the tubular lumen. HE, obj.40x.

Discussion

The diagnosis of renal encephalopathy due to acute renal failure induced by administration of sulfadiazine was based on clinical-pathologic findings. Renal encephalopathy is uncommon in domestic animals and there is only one report of this condition in goats, caused by diffuse, severe tubular and glomerular necrosis and degeneration of undetermined cause (11).

The pathophysiology of renal encephalopathy is complex and poorly understood. Accumulation of metabolites, hormones, disturbance in the intermediary metabolism and imbalance between excitatory and inhibitory neurotransmitters have been pointed as contributing factors (3). Renal failure results in accumulation of numerous organic substances that may act as uremic neurotoxins, but no single metabolite has been identified as the sole cause of renal failure (4). Some of the metabolites that accumulate include urea, guanidino compounds, uric acid, several amino acids and polypeptides (3, 4). As in this case where high level of creatinine were found, in uremic human patients the creatinine was highly increased in serum, cerebrospinal fluid and brain (7). It is postulated that these compounds may contribute to the clinical signs accompanying uremic encephalopathy (3, 4, 7).

Histologically, the distribution of spongy degeneration in the brain of this goat is characteristic both of renal and hepatic encephalopathy in ruminants (13). Since no hepatic lesions were observed in the goat of this report, it's been assumed that the severe renal lesions were responsible for the renal encephalopathy. The typical histological lesion observed in these cases is polymicrocavitation or status spongiosus of the white matter and it typically involves myelinated bundles of fibers that are interspersed with gray matter (13). Vacuolated myelin appears to be stable, does not incite microglial response, and can be viewed as a form of cytotoxic edema. The spongiotic change results from intramyelinic edema (vacuolation) or results from swelling of the outer tongue of oligodendrocyte cytoplasm (9). In humans and horses other typical changes are solitary or small groups of astrocytes with clear, swollen nuclei, known as Alzheimer type II cells (9, 13). No such cells were present in this case. In horses, changes are limited to the development of Alzheimer type II cells and were reported associated with renal encephalopathy (5). In other species such as ruminants the polymicrocavitation is the most obvious alteration, and sometimes it is the sole lesion observed (13).

The severe renal tubular lesions in this case were most likely responsible for induction of renal encephalopathy. Sulfonamide toxicity was concluded to be the cause of toxic tubular necrosis. Nephrotoxicity associated with sulfonamides is rare as most of the current pharmaceutical preparations are relatively highly soluble at the normal renal pH (12). In this case the kind of sulfonamide used was sulfadiazine. A major side effect of sulfadiazine therapy is the occurrence of crystallization in the urinary collecting system (12). A case of an AIDS patient with toxoplasmic encephalitis treated with sulfadiazine who developed acute renal failure is reported (10). Severe nephropathy may be caused by an overdose of sulfonamide or when the animal is dehydrated (8), as was the case in this goat which was dehydrated due to diarrhea caused by *Eimeria* spp. Animals with toxic nephropathy will show elevated levels of BUN and creatinine (15), as seen in this case. In some animals sulfonamide crystals may be observed grossly in the renal pelvis (12). However, no gross lesions were observed in this case. It's supposed that the renal lesions are due both to local toxic and

mechanical (tubule-obstructive) effects (12). Although acute renal failure is a common affection in domestic animals, rarely it develops in renal encephalopathy.

Differential diagnoses for CNS disease in this goat included scrapie, caprine arthritis encephalitis, rabies, heavy-metal toxicosis (lead), copper deficiency, storage diseases (mannosidosis), polioencephalomalacia, listeriosis, *Histophilus somni* infection, hepatic and renal encephalopathy and pregnancy toxemia (9).

Renal encephalopathy is rarely reported in small ruminants. We report here a case of renal encephalopathy associated with status spongiosus due to severe acute renal failure in a goat treated with sulfadiazine.

References

1. ANDERSON WI., De LAHUNTA A., HORNBUCKLE WE., KING JM., TENNANT BC. Two cases of renal encephalopathy in the woodchuck (*Marmota monax*). **Lab. Anim. Sci.**, 1990, 40, 86-88.
2. BOUCHARD PR., WELDON AD., LEWIS RM., SUMMERS BA. Uremic encephalopathy in a horse. **Vet. Pathol.**, 1994, 31, 111-115.
3. BROUNS R., De DEYN PP. Neurological complications in renal failure: a review. **Clin. Neurol. Neurosurg.**, 2004, 107, 1-16.
4. FRASER CL., ARIEFF AI. Metabolic encephalopathy as a complication of renal failure: mechanisms and mediatiors. **New Horiz.**, 1994, 2, 518-526.
5. FRYE MA., JOHNSON JS., TRAUB-DARGATZ JL., SAVAGE CJ., FETTMAN MJ., GOULD DH. Putative uremic encephalopathy in horses: five cases (1978-1998). **J. Am. Vet. Assoc.**, 2001, 218, 560-566.
6. KANEKO JJ., HARVEY JW., BRUSS ML. Appendix VIII blood analyte reference values in large animals. In Ibid (Ed) **Clinical Biochemistry of Domestic Animals**. 6 ed. Elsevier, San Diego 2008: 882-888.
7. MAHONEY CA., ARIEFF AI. Uremic encephalopathies: clinical, biochemical, and experimental features. **Am. J. Kidney Dis.**, 1982, 2, 324-336.
8. MAXIE MG., NEWMAN SJ. Urinary system. MAXIE MG. (Ed). **Jubb, Kennedy, and Palmer's Pathology of Domestic Animals**. 5 ed., vol. 2. Saunders Elsevier, Philadelphia 2007: 425-522.
9. MAXIE MG., YOUSSEF S. Nervous system. MAXIE MG. (Ed). **Jubb, Kennedy, and Palmer's Pathology of Domestic Animals**. 5 ed., vol. 1. Saunders Elsevier, Philadelphia 2007: 281-457.
10. PRADA AFJ., PRADOS GAM., TUGORES VA., URIOL RM., MOREY MA. Acute renal failure due to sulfadiazine crystalluria. **An. Med. Interna.**, 2007, 24, 235-238.
11. RADI ZA., THOMSEN BV., SUMMERS BA. Renal (uremic) encephalopathy in a goat. **J. Vet. Med.**, 2005, 52, 397-400.
12. SEBASTIAN MM., BASKIN SI., CZERWINSKI SE. Renal toxicity. GUPTA RC. (Ed). **Veterinary Toxicology**. Saunders Elsevier, New York 2007: 161-176.
13. SUMMERS BA., CUMMINGS JF., De LAHUNTA A. Degenerative diseases of the central nervous system. In Ibid (Ed). **Veterinary Neuropathology**. Mosby, Saint Louis 1995: 208-350.
14. SUMMERS BA., SMITH CA. Renal encephalopathy in a cow. **Cornell Vet.**, 1985, 75, 524-530.
15. VERDESCA S., CUCCHIARI D., MONARI M., PODESTÀ MA., BADALAMENTI S. Sulfamethoxazole crystalluria. **G. Ital. Nefrol.**, 2015, 32, 32-35.
16. WOLF AM. Canine uremic encephalopathy. **J. Am. Anim. Hosp. Assoc.**, 1980, 16, 735-738.