Uremic encephalopathy in a rhesus macaque (*Macaca mulatta*), a case report and a brief review of the veterinary literature

Allison Mustonen^{1,2}, Olga Gonzalez¹, Elda Mendoza¹, Shyamesh Kumar¹, and Edward J. Dick Jr.¹

¹Southwest National Primate Research Center at the Texas Biomedical Research Institute, San Antonio, TX, USA

²College of Veterinary Medicine, Purdue University, West Lafayette, IN, USA

Abstract

Background—Uremic encephalopathy is uncommon, yet is one of the most severe complications of renal failure. We present a case of acute renal failure and associated cerebral and vascular lesions consistent with uremic encephalopathy in a rhesus macaque (*Macaca mulatta*).

Methods—A 14 year old, female, specific-pathogen-free rhesus macaque presented in lateral recumbency, obtunded, severely dehydrated, and hypothermic, with severe azotemia, mild hyponatremia, hypokalemia, hypochloremia, increased anion gap, and hypercholesterolemia. Due to poor prognosis, the animal was euthanized and a complete necropsy was conducted.

Results—The animal had diffuse proximal renal tubular epithelial necrosis and loss; regeneration of tubular epithelium was not observed. There was bilateral necrosis and loss of neurons and glial cells in the hippocampus and deep cerebral cortex with edema and multifocal areas of hemorrhage.

Conclusion—We present the first reported case of uremic encephalopathy in a rhesus macaque and describe the associated cerebral and vascular lesions.

Keywords

Renal Insufficiency; Acute Kidney Injury; Uremia; Brain Diseases

Introduction

Acute renal failure (ARF) is a severe disease across species, and is defined as an abrupt deterioration of renal function sufficient to result in failure of urinary elimination of nitrogenous waste products such as urea and creatinine [1]. In humans, this condition is associated with a mortality rate of 20–75% [2]. ARF has been classified as pre-renal, renal (intrinsic), and post renal [2]. Pre-renal ARF is due to hypovolemia and decreased renal vascular perfusion [2]. Renal ARF is due to direct damage to nephrons, resulting in a functional loss of concentrating ability and decreased elimination of metabolic waste

Corresponding Author: Shyamesh Kumar, DVM, PHD, Diplomate ACVP, Southwest National Primate Research Center, Texas Biomedical Research Institute, P.O. Box 760549, San Antonio, Texas, 78245-0549 USA, Tel: 210 258 9704; Fax: 210 670 3305; shykumar@txbiomed.org.
DR. SHYAMESH KUMAR (Orcid ID : 0000-0001-9261-2263)

products (azotemia) [2, 3]. Pre-renal and renal ARF are often concurrent and together account for more than 75 % of cases of ARF in humans [2, 4]. In contrast, post-renal ARF is due to occlusion of the urethra or ureters, resulting in increased pressure in collecting ducts, reduced GFR and renal failure [2] [3].

Etiologically, the main causes of ARF can be summarized into three groups: physiologic, toxic, and infectious. Physiologic causes include renal ischemia due to hypovolemia, decreased cardiac output, increased blood viscosity, and altered renal and/or systemic vascular resistance [2, 5]. The list of toxic causes, especially in veterinary medicine, is exhaustive and ever expanding, and includes nephrotoxic medications such as antimicrobials, chemotherapy drugs, and NSAIDs as well as toxicants such as ethylene glycol, melamine, lead, toxic plants, excess vitamin D, excess hemoglobin from intravascular hemolysis, and excess serum myoglobin due to rhabdomyolysis [3, 6]. Infectious etiologies reported to cause renal failure include *Escherichia coli*, *Streptococcus sp.*, *Leptospira sp.*, and rickettsial diseases [3, 6, 7]. If the animal survives and the ARF leads to uremia, subsequent lesions may include stomatitis, glossitis, gastritis, pulmonary edema, fibrinous pericarditis, atrial thrombosis, coagulopathy, and soft tissue mineralization [2, 5].

Uremic encephalopathy is one of the most severe complications of renal failure (both acute and chronic) in humans [8]. It is characterized by a spectrum of clinical signs such as convulsions, seizures, and lack of cognitive ability [9, 10]. Associated lesions include neuronal necrosis, cerebral edema, neuropil vacuolation, vascular thrombosis, hemorrhage, and arterial fibrinoid necrosis [10]. In veterinary medicine, uremic encephalopathy has been reported in dogs, cattle, horses, woodchucks, goats, and a coyote [11–16]. We present the first reported case of acute renal failure and associated cerebral and vascular lesions consistent with uremic encephalopathy in a rhesus macaque (*Macaca mulatta*) and a brief review of veterinary literature. To the best of our knowledge, this is the first report of uremic encephalopathy in nonhuman primates.

Materials and Methods

Animal

The macaque was socially housed in metal and concrete indoor/outdoor enclosures, fed a commercial diet (5LE0, Purina, St Louis, MO) supplemented with grains, vegetables, and fruits, and water was provided *ad libitum*. This animal was part of a breeding colony specific-pathogen-free (SPF) for Simian Retrovirus type D (SRV-D), Macacine herpesvirus 1 (Herpesvirus simiae, B virus), Simian immunodeficiency virus (SIV), and Simian T-lymphotropic virus (Simian T cell leukemia virus, STLV-1), and not used for experimental purposes. All animal care and procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee.

Pathology

A complete necropsy was performed, and appropriate tissue samples were taken for histologic evaluation. All tissues were fixed in 10% neutral buffered formalin, processed

conventionally, embedded in paraffin, cut at 5 microns, stained with hematoxylin and eosin, and evaluated by light microscopy by a board-certified veterinary pathologist.

Case report

Presentation

The 14 year old, female, SPF rhesus macaque was presented to the hospital with a history of lateral recumbency in the cage, diarrhea, weight loss, dehydration, vomiting, lethargy, and not responding to any stimulus. The animal was treated with metronidazole (Oakdell Pharmacy, San Antonio, TX, 30mg/Kg BID PO) enrofloxacin (Baytril 2.27%, Bayer AG, Leverkusen, Germany, 20ml, IV), and aggressive intravenous and subcutaneous supportive fluid therapy. The animal's condition continued to deteriorate, and on the second day, the serum biochemistry indicated severe azotemia (BUN = 294 mg/dL, reference range; 13 – 23 mg/dL, creatinine = 7.0 mg/dL, reference range; 0.5 – 1.0 mg/dL), mild hyponatremia (128 meq/L, reference range; 137–149 meq/L), hypokalemia (1.9 meq/L, reference range; 2.9 – 4 meq/L), hypochloremia (97 meq/L, reference range; 105 – 116 meq/L), increased anion gap (25.9 meq/L, reference range; 9 – 16 meq/L), and hypercholesterolemia (208 mg/dL, reference range; 84–194 mg/dL). Calcium and phosphorus levels were within normal limits. A complete blood count indicated a mild polycythemia, and a stress leukogram characterized by leukocytosis, mature neutrophilia, lymphopenia, eosinopenia, and monocytosis. Due to the poor clinical prognosis and deteriorating condition, the macaque was humanely euthanized and necropsied 30 minutes later.

Gross pathology

The animal had adequate muscle and hydration with scant adipose tissue. There were mucosal sloughing and ulcerations along the lower lip margin, upper lip, and tip of the tongue (Figure 1. A–B). There were multifocal, patchy petechiae and ecchymoses throughout the haired skin of the proximal extremities and abdominal and inguinal regions (Figure 1.C). The gastric mucosa was edematous and there were multifocal to coalescing petechial hemorrhages throughout the gastric fundus and along the greater and lesser curvature (Figure 1.D). The colon contents were tan to red, liquid and mucoid. The kidneys were diffusely pale tan. There were bilateral symmetrical soft dark brown foci in the hippocampus and extending towards the midline (basal nucleus) suggestive of hemorrhage, and malacia (Figure 2.A).

Histopathology

The kidneys had diffuse proximal tubular epithelial necrosis and loss; remaining tubular epithelium exhibited variable vacuolar degeneration and cytoplasmic eosinophilia. Multifocally, tubules were dilated, and lined by flattened, attenuated cells (Figure 2.B). Regeneration of tubular epithelium was not observed. The tubular lumina contained cellular debris, rare neutrophils, protein casts, and mineralized concretions. Within the brain, the hippocampus was most severely affected. There were bilateral, locally extensive areas of necrosis and hemorrhage, with extensive edema, vacuolation of neuropil, and necrosis of neurons in the dentate gyrus (Figure 3.C). Individual pyramidal neurons were multifocally shrunken and hypereosinophilic, with pyknotic or karyorrhectic nuclei (necrotic). Multifocal

paired astrocytes with swollen, enlarged nuclei and clear chromatin were present in the hippocampus and affected areas of grey matter (Alzheimer type II astrocytes, Figure 3.D). Multifocally, within the deep cerebral cortex, individual neurons were shrunken, and had hypereosinophilic cytoplasm and pyknotic nuclei (necrosis); the adjacent white matter neuropil had focally extensive areas of edema, vacuolization and mild disruption of myelin (Figure 3.E). The tongue and lips had multifocal mucosal ulcers and erosions which were covered by a thick mat of fibrin, neutrophils, necrotic debris, and a mixed population of bacteria. The haired skin of the axillary and inguinal regions had acute dermal hemorrhages, vascular fibrinoid necrosis, and mild neutrophilic vasculitis. The gastric mucosa had multifocal to coalescing areas of epithelial necrosis, with submucosal vascular fibrinoid necrosis (Figure 3.F), neutrophilic vasculitis, and submucosal edema. There were moderate numbers of neutrophils, fewer lymphocytes and plasma cells throughout the lamina propria with frequent necrosis of gastric glands. The colonic mucosa had extensive necrosis and regional glandular epithelial atrophy and regeneration with increased glandular epithelial mitosis. The colonic lamina propria was diffusely expanded by lymphocytes, plasma cells, macrophages, and neutrophils extending to the base of the glands and in the submucosa.

Additional diagnostic testing

The colonic contents tested negative for *Shigella flexneri* by PCR (Zoologix Inc, CA), and aerobic culture of the colonic contents failed to identify pathogenic bacteria. Serology and viral cultures from oral ulcers, conjunctiva and genitalia were negative for Herpes B virus at the National B Virus Resource Center, Georgia State University (<http://www2.gsu.edu/~wwwvir/index.html>).

Discussion

The acute onset of clinical signs, hematologic and serum biochemistry findings, and spectrum of gross and histopathological lesions in this case are consistent with ARF and uremic encephalopathy. Central nervous system lesions in this case included bilateral hippocampal and deep cortical neuronal necrosis and loss, with multifocal vacuolation of the white matter neuropil, perivascular and perineuronal edema, and congestion and hemorrhage of small blood vessels. The cause of acute renal failure remains undetermined, but most likely resulted from combined pre-renal and renal events (i.e. hypovolemia, severe dehydration, diarrhea, ischemia and possible septicemia), leading to precipitous clinical deterioration. We speculate that given the clinical history of diarrhea and dehydration, ischemic necrosis due to hypovolemia was the most likely cause of ARF. Sepsis along with hypovolemia and continued water loss due to diarrhea could have exacerbated hemodynamic injury to the kidney. Toxic etiologies were considered unlikely based on clinical history, lack of affected cagemates, and the fact that the animal was cage housed with limited access, and no history of exposure, to any known toxicant or drug. The antibiotics used (metronidazole and enrofloxacin) are not primarily nephrotoxic. The definite cause of the diarrhea could not be determined in this case.

The pathophysiology of the uremic encephalopathy is complex and multi-factorial. Some of the proposed mechanisms include accumulation of harmful metabolites (uremic toxins such

as creatinine, guanidine, guanidinosuccinic acid, and methyl guanidine), disturbances of energy metabolism (decreased levels of creatine phosphate, ATP, and glucose, and increased levels of AMP, ADP, and lactate), imbalance between excitatory and inhibitory neurotransmitters (N-methyl-D-aspartate receptor [NMDA] vs gamma-aminobutyric acid [GABA]), oxidative stress (increased reactive oxygen species), and hormonal imbalances (elevated parathyroid hormone level) [9, 10, 17]. Uremia results in inappropriate activation of excitatory NMDA receptors and concomitant inhibition of inhibitory GABA neurotransmitters, resulting in excitatory neurotoxicity, and is one of the accepted mechanisms of uremic encephalopathy [17]. Neuronal excitotoxicity has also been proposed as a mechanism of neuronal necrosis in cats with chronic seizure [18, 19], and resulted in lesions similar those observed in this macaque. Although the underlying toxic metabolite has not been identified, human patients with uremic encephalopathy typically show improved neurological symptoms after dialysis treatment [20].

ARF is a pro-inflammatory state, and leads to systemic coagulopathy through various mechanisms including loss of antithrombin III, platelet activation, abnormal platelet-endothelial interaction, and several unexplained pathways, together leading to disseminated intravascular coagulation and fibrinoid necrosis of the microvasculature, with superficial ecchymoses and petechial hemorrhages of the skin and gastric mucosa [21, 22]. The oral ulcerations noted in this case were likely due to irritation of the mucosa from ammonia compounds formed by hydrolysis of urea in the saliva by urease producing bacteria in the oral cavity.

Uremic encephalopathy is a clinical condition, well reported in humans, and is characterized by signs such as mild to severe loss of cognitive abilities, loss of sustained posture (asterixis), tremors, myoclonus, tetany, motor abnormalities and convulsions [11, 23]. Among veterinary species, spontaneous cases of uremic encephalopathy have been reported in dogs, cattle, horses, woodchucks, goats, and a coyote [11–16, 24–26]. Clinical signs include anorexia, dehydration, depression, ataxia, blindness, tremors, and sudden death [11–16]. Laboratory findings include moderate to severe azotemia [11–16]. Veterinary case reports describe variable presentations of nervous lesions. Large areas of vacuolar degeneration of the cerebral white matter (spongiform change/intramyelinic edema) with the presence of swollen astrocytes having clear chromatin (Alzheimers type II astrocytes) have been reported in some cases [11, 12]; other reports lacked the presence of Alzheimers type II astrocytes [13, 15, 24, 25]. It has been alluded that the Alzheimers type II astrocytes may be a more prevalent feature of uremic encephalopathy in horses [11]. Rosa *et al* and Hasel *et al* reported localized vacuolar degeneration of the basal ganglia and hippocampus [15, 27]. Dunigan *et al* did not identify any gross or histopathological lesion in the nervous system, and based upon clinical signs and renal lesions, diagnosed the case as an “apparent” renal encephalopathy in a cow [16]. The veterinary literature contains examples of both acute [13, 15, 16] and chronic kidney disease [12, 24, 25] resulting in encephalopathy and, with the exception of a goat in which sulfonamide toxicity was concluded to be the cause [15], the inciting cause of acute renal failure was usually unidentified.

Uremic encephalopathy is an uncommon condition in animals with a variable spectrum of histopathological lesions. We present the first reported case of uremic encephalopathy in a

rhesus macaque, and describe the associated cerebral and vascular lesions. To the best of our knowledge, this is the first report of uremic encephalopathy in nonhuman primates. This condition should be considered during the management of ARF in non-human primates.

Acknowledgments

The authors wish to thank the residents and the staff pathologists at Joint Pathology Center, MD, for their assistance with this case. The authors express sincere gratitude to Sarah Pennington, Jesse Martinez, Antonio “Tony” Perez, and Renee Escalona for their anatomic pathology support and the clinical support staff of the Texas Biomedical Research Institute. This investigation used resources which were supported by the Southwest National Primate Research Center grant P51 RR013986 from the National Center for Research Resources, National Institutes of Health and which are currently supported by the Office of Research Infrastructure Programs through P51 OD011133 and was conducted in facilities constructed with support from the Office of Research Infrastructure Programs (ORIP) of the National Institutes of Health through Grant Number C06 RR017332.

References

1. Dwinnell BGAR. Atlas of Diseases of Kidney. Philadelphia: Current Medicine Inc; 1999. Diagnostic evaluation of the patient with acute renal failure; 1–12.
2. Singh AP, Muthuraman A, Jaggi AS, Singh N, Grover K, Dhawan R. Animal models of acute renal failure. *Pharmacological Reports*. 2012; 64:31–44. [PubMed: 22580518]
3. Stokes JE, Bartges JW. Causes of Acute Renal Failure. *VetFolio*. 2006; 28:11.
4. Lameire N, Van Biesen W, Vanholder R. The changing epidemiology of acute renal failure. *Nature clinical practice Nephrology*. 2006; 2:364–377.
5. Breshears MA, Confer AW. The Urinary System. In: Zachary JM, editor *Pathologic Basis of Veterinary Disease*. St. Louis, MO: Elsevier; 2017. 622–623.
6. Stokes JE, Forrester SD. New and unusual causes of acute renal failure in dogs and cats. *The Veterinary clinics of North America Small animal practice*. 2004; 34:909–922. vi. [PubMed: 15223208]
7. Zech P, Rife G, Lindner A, Sassard J, Blanc-Brunat N, Traeger J. Malignant hypertension with irreversible renal failure due to oral contraceptives. *BMJ*. 1975; 4:326–327.
8. Seifter J, Samuels M. Uremic Encephalopathy and Other Brain Disorders Associated with Renal Failure. *Seminars in Neurology*. 2011; 31:139–143. [PubMed: 21590619]
9. Scaini G, Ferreira GK, Streck EL. Mecanismos básicos da encefalopatia urêmica. *Revista Brasileira de Terapia Intensiva*. 2010; 22:206–211. [PubMed: 25303764]
10. Nongnuch A, Panorchan K, Davenport A. Brain-kidney crosstalk. *Critical care*. 2014; 18:225. [PubMed: 25043644]
11. Bouchard PR, Weldon AD, Lewis RM, Summers BA. Uremic Encephalopathy in a Horse. *Veterinary Pathology*. 1994; 31:111–115. [PubMed: 8140716]
12. Frye MA, Johnson JS, Traub-Dargatz JL, Savage CJ, Fettman MJ, Gould DH. Putative uremic encephalopathy in horses: five cases (1978–1998). *Journal of the American Veterinary Medical Association*. 2001; 218:560–566. [PubMed: 11229510]
13. Radi ZA, Thomsen BV, Summers BA. Renal (Uremic) Encephalopathy in a Goat. *Journal of Veterinary Medicine Series A*. 2005; 52:397–400. [PubMed: 16176568]
14. Shimada A, Kuwamura M, Awakura T, Umemura T, Yamane Y. Spongiform Degeneration of the Brain Associated with Uremia in an Aged Coyote (*Canis latrans*). *Veterinary Pathology*. 1994; 31:484–487. [PubMed: 7941243]
15. Rosa F, Rubin M, Leal PV, Martins TB, Carlotto Gomes D, Araújo MA, Lemos RAA, Barros CSL. Renal encephalopathy due to acute renal failure in a goat. 2015
16. Dunigan C, Tyler J, Valdez R, Messinger M, Schott H, Parish S, Talcott P. Apparent renal encephalopathy in a cow. *Journal of veterinary internal medicine*. 1996; 10:39–41. [PubMed: 8965267]
17. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. *Clinical neurology and neurosurgery*. 2004; 107:1–16. [PubMed: 15567546]

18. Fatzer R, Gandini G, Jaggy A, Doherr M, Vandewelde M. Necrosis of hippocampus and piriform lobe in 38 domestic cats with seizures: a retrospective study on clinical and pathologic findings. *Journal of veterinary internal medicine*. 2000; 14:100–104. [PubMed: 10668825]
19. Fors S, Van Meervenne S, Jeserevics J, Rakauskas M, Cizinauskas S. Feline hippocampal and piriform lobe necrosis as a consequence of severe cluster seizures in two cats in Finland. *Acta veterinaria Scandinavica*. 2015; 57:41. [PubMed: 26215252]
20. Van Dijck A, Van Daele W, Paul D. Uremic Encephalopathy. 2012.
21. Salman . Uremic Bleeding: A Concise Review. *The Journal of Tepecik Education and Research Hospital*. 1994; 4:7–13.
22. Conlon PJ, Howell DN, Macik G, Kovalik EC, Smith SR. The renal manifestations and outcome of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in adults. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 1995; 10:1189–1193.
23. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. *JRSM cardiovascular disease*. 2016; 5:2048004016677687. [PubMed: 27867500]
24. Summers BA, Smith CA. Renal encephalopathy in a cow. *The Cornell veterinarian*. 1985; 75:524–530. [PubMed: 4053611]
25. Anderson WI, deLahunta A, Hornbuckle WE, King JM, Tennant BC. Two cases of renal encephalopathy in the woodchuck (*Marmota monax*). *Laboratory animal science*. 1990; 40:86–88. [PubMed: 2153871]
26. Wolf AM. Canine uremic encephalopathy. *Journal American Animal Hospital Association*. 1980
27. Hasel KM, Summers BA, Lahunta A. Encephalopathy with idiopathic hyperammonaemia and Alzheimer type II astrocytes in Equidae. *Equine Veterinary Journal*. 1999; 31:478–482. [PubMed: 10596928]

Figure 1.
(A–D). Gross lesions. **A & B.** Ulceration of the upper lip and tongue. **C.** Ecchymosis and petechiation of the inguinal haired skin. **D.** Hemorrhage and ulceration of the gastric mucosa.

Figure 2.

(A–F). Gross lesion. **A.** Coronal sections of the brain, showing bilateral dark discoloration of hippocampus and surrounding parenchyma suggestive of hemorrhage and malacia. Histologic lesions. **B.** Kidney: diffuse dilation of the renal tubules lined with flattened and attenuated cells. Necrosis and loss of tubular epithelium, and lumina containing sloughed epithelial cells. **C.** Hippocampus: localized extensive area of necrosis, hemorrhage, and edema. **D.** Higher magnification showing necrosis with vacuolation, nuclear pyknosis, and neuronal loss, with few scattered Alzheimer type II astrocytes (arrow). **E.** Deep cerebral cortex: spongy degeneration and vacuolization of the white matter and multifocal neuronal necrosis in grey matter. **F.** Large caliber artery in the gastric submucosa with fibrinoid necrosis and mild neutrophilic vasculitis.