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Putative uremic encephalopathy in horses: five cases (1978–1998)

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EQUINE

Objective—To determine historical, physical examination, clinicopathologic, and postmortem findings in horses with putative uremic encephalopathy.

Design—Retrospective study.

Animals—5 horses with renal failure and neurologic disease not attributable to abnormalities in any other organ system.

Procedure—Medical records from 1978 to 1998 were examined for horses with renal disease and neurologic signs not attributable to primary neurologic, hepatic, or other diseases. Signalment, history, physical examination findings, clinicopathologic data, renal ultrasonographic findings, and postmortem data were reviewed.

Results—Of 332 horses with renal disease, 5 met selection criteria. Historical findings, physical examination findings, clinicopathologic data, ultrasonographic data, and postmortem findings were consistent with chronic renal failure. Swollen astrocytes were detected in all 4 horses examined at necropsy.

Conclusions and Clinical Relevance—A single criterion was not determined to be pathognomonic for uremic encephalopathy in horses. Uremic encephalopathy should be considered as a differential diagnosis in horses with evidence of chronic renal failure and encephalopathic neurologic sign not attributable to other causes. Astrocyte swelling, which was common to all 4 horses examined at necropsy, may serve as a microscopic indicator of uremic encephalopathy in horses. (*J Am Vet Med Assoc* 2001;218:560–566)

Uremic encephalopathy (UE) has been recognized in humans since 1831.[1] Despite continued attempts to elucidate the cause of the syndrome, pathophysiologic features remain poorly defined. Because of this, and lack of pathognomonic signs or laboratory data,[1] UE is a diagnosis made by eliminating other causes of neurologic disease. Uremic encephalopathy occurs in humans with acute or chronic renal failure. In humans with acute renal dysfunction, the syndrome is often more severe and rapidly progressive than in those with chronic disease.[2] In addition, human patients with acute renal dysfunction have clinical signs of UE associated with lower plasma urea concentrations than those of patients with chronic disease.[3] Early signs of UE in humans may include malaise, impaired concentration, insomnia, fatigue, apathy, dysarthria, tremors, asterixis,[1] weakness, nystagmus, and facial asymmetry.[3] Later manifestations of the syndrome in humans may include defective cognition, hallucinations, agitation, myoclonus, tetany, bizarre behavior, delirium, convulsions, stupor, coma, and death.[1] If the acute renal failure resolves or dialysis is instituted, signs and symptoms may diminish; however, some subtle neurologic symptoms may persist.[3]

Uremic encephalopathy has been described in several animal species, including dogs,[4] cattle,[5,6] and woodchucks.[7] One case report of the syndrome in horses has been published.[8] Signs of UE were not described in a 32-year retrospective study[9] that characterized the prevalence and signs of chronic renal failure in horses. The purpose of the study reported here was to describe the historical, physical examination, clinicopathologic, and postmortem findings associated with putative UE in horses.

Criteria for Selection of Cases

A computer search of the medical record database of equine patients examined at the **Colorado State University Veterinary Teaching Hospital (CSU-VTH)** during a 20-year period (1978 to 1998) was undertaken to identify horses with renal disease and neurologic signs not attributable to hepatoencephalopathy or a specific neurologic lesion or site.

Procedures

Data derived from the medical records included age, breed, sex, historical and physical abnormalities, clinically defined neurologic deficits, pertinent clinicopathologic data (BUN concentration; serum creatinine concentration; sodium, potassium, chloride, calcium, and bicarbonate concentrations; hepatic enzyme activity; total bilirubin and bile acid concentrations; ammonia concentration; urinalysis; urine **γ-glutamyl transferase (GGT)**-to-creatinine ratio; urinary fractional excretions of sodium, chloride, and potassium; PCV; total protein concentration, outcome (discharged alive, died, euthanatized), and postmortem findings, if available. Renal disease was classified as acute or chronic on the basis of clinical data, laboratory tests, and interpretation of pathologic findings. Postmortem examination was performed on 4 of 5 horses. Histologic sections of kidney and brain were reviewed. Freshly prepared 4- to 5-µm sections cut from paraffin blocks were stained with H&E; separate sections were prepared for **glial**

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fibrillary acidic protein (GFAP) immunohistochemical staining.

Brain sections were compared with those of 4 horses (age, 2 to 17 years) that were necropsied at the CSU-VTH Diagnostic Laboratory and that did not have clinical history or signs of neurologic, renal, or hepatic disease. Brains were removed and immersion-fixed in neutral-buffered 10% formalin for > 48 hours. Sections were cut from similar anatomic locations as from affected horses, embedded in paraffin, and sectioned, as described.

One slide of cerebral cortex from each of the horses with putative UE and the 4 control horses was used for measuring nuclear diameter of astrocytes. Tagged image files were captured by use of a digital camera and analyzed by use of computer software.[a] A minimum of 60 astrocyte nuclei from 10 or more randomly selected fields of the submeningeal cortical gray matter were measured for each horse. The nuclear diameters of the 60 astrocytes were compared between control horses and those with putative UE by use of a statistical software program[b] to perform a 2-sample unpaired *t*-test.

Paraffin sections for immunohistochemical examination were dewaxed in 2 changes of xylene for 5 minutes each and hydrated through graded alcohols. Slides were stained by use of an automated immunohistochemistry system.[c] Slides were rinsed and incubated for 32 minutes at 37 C with a polyclonal rabbit anti-human antiglial fibrillary acidic protein primary antibody.[d] Universal secondary antibody,[c] goat anti-mouse and goat anti-rabbit IgG, and goat anti-mouse IgM were applied and incubated at 37 C. Slides were washed and streptavidin-alkaline phosphatase conjugate[c] was applied and incubated for 12 minutes at 37 C followed by enhancer for 4 minutes at 37 C. Fast Red A and naphthol[c] were applied and slides were incubated for 8 minutes at 37 C followed by application of Fast Red B[c] for 8 minutes at 37 C. A negative control slide was made by use of a rabbit polyclonal antibody contained in nonimmune sera[c] in place of the primary antibody to detect nonspecific immunoglobulin staining.

Immunohistochemical stains were examined for comparison of staining intensity. One slide from each horse with putative UE was compared with a slide from an anatomically similar location (cerebral cortex, basal ganglia, hippocampus, midbrain, medulla oblongata, and cerebellum) in the 4 control horses. The slides were labeled in a manner that prevented identification of individual horses by the pathologists (DHG, JSJ). Slides were ranked from 1 to 8 on the basis of staining intensity for GFAP in submeningeal gray matter. A score of 1 indicated the most prominent staining.

To determine influence of duration of storage of paraffin-embedded nervous tissue on GFAP immunoreactivity, brain sections from archived paraffin blocks of 4 horses, which had been stored since 1982 and 1988, were compared with slides from 2 of the 4 unaffected control horses and horses with putative UE. Slides were batch-stained for GFAP reactivity. Sections examined included those from cerebral cortex and cerebellum. Two GFAP-negative control slides were included to determine the presence of nonspecific staining. Primary antibody was omitted in the first negative control slide, and in the second control slide it was replaced with a rabbit polyclonal antibody contained in nonimmune sera[c] to detect nonspecific immunoglobulin staining.

Results

Three hundred and thirty-two patient records were identified that described some type of renal lesion or pathologic change. Of these 332 horses, 40 had concomitant neurologic signs. All but 5 of these horses were excluded from the study on the basis of nonrenal diseases that may have induced the neurologic signs (eg, severe colic, colitis, hepatic disease, endotoxemia, severe metabolic abnormalities not attributable to renal failure [eg, acidemia, electrolyte disturbances], and primary neurologic disease). Neurologic diagnoses included equine protozoal myeloencephalitis, hypoxemic-ischemic encephalopathy of foals, cerebellar abiotrophy, cauda equina neuritis, and gross lesions of the brain and spinal cord.

Horses that met selection criteria ranged in age from 2 to 20 years (median, 5 years). Breeds represented included Arabian, Quarter Horse, and Friesian. All horses were sexually intact, and 3 of the 5 were female. Clinical signs reported in the medical history in 2 or more horses, in order of frequency, included ataxia or weakness, weight loss or ill thrift, and anorexia. Various signs of cerebral dysfunction were reported in 4 of the 5 horses and included obtunded mentation, lethargy, head pressing, signs of anxiety, and apparent changes in cognition.

At the time of physical examination at CSU-VTH, all horses were substantially azotemic. Electrolyte abnormalities included, in order of frequency, hypochloremia, hyperkalemia, hypercalcemia, hypophosphatemia, hyponatremia, hypernatremia, and hyperphosphatemia. Low serum bicarbonate or total carbon dioxide concentrations were found in 3 of 4 horses. Urinalyses were performed on 3 horses, and all were isosthenuric (pH, 1.008 to 1.014). Blood or hemoglobin (2 to 4+) was detected in urine of all 3 horses. Urinary fractional excretions of sodium, chloride, or potassium were determined for 2 horses; fractional excretion of sodium ranged from 2 to 3% (reference limit, < 1%), and fractional excretion of potassium ranged from 117.5 to 283.0% (reference range, 15 to 65%), consistent with renal tubular damage. Bacteriologic cultures of urine or renal tissue were not performed in any horse.

Renal ultrasonography was performed in 2 of 5 horses. Poor corticomedullary differentiation was detected in both horses and was attributed to chronic renal disease. Hyperechoic density with shadowing was observed in both kidneys of these 2 horses, indicating dystrophic calcification, small calculi, or both.

Cerebrospinal fluid was obtained from the lumbosacral space of 2 of the 5 horses with putative UE. Results of analysis of CSF were considered nondiagnostic in 1 horse because of blood contamination. Results of CSF analysis in the other horse were within reference ranges.

One horse died spontaneously, and 4 horses were euthanatized. One horse was euthanatized within 24

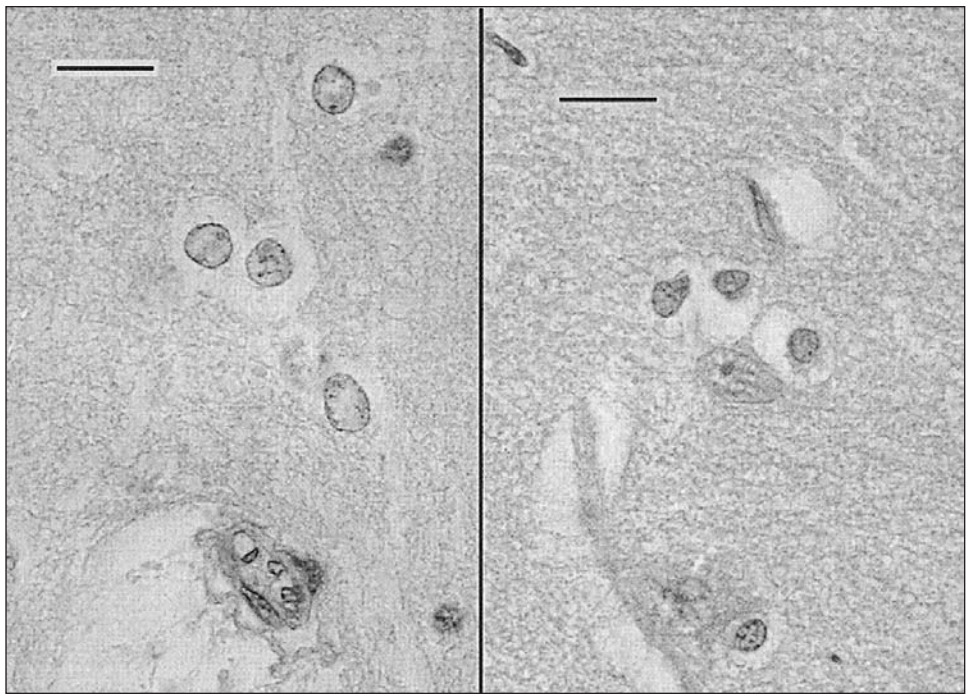

Figure 1—Photomicrographs of a section of cerebral cortex from a horse with putative uremic encephalopathy (left) and from a healthy control horse (right). Notice that astrocytes in the cerebral cortex of the horse with putative uremic encephalopathy have swollen nuclei with chromatin dispersed to the periphery of the nucleus. H&E stain; bar = 20 μm.

hours of admission because of deteriorating condition (unspecified) and poor prognosis. Treatment had not been performed. Another horse was euthanatized within hours of admission because of poor prognosis. No treatment had been initiated. A third horse was euthanatized within hours of admission because of development of head pressing, nystagmus, recumbency, obtunded mentation, and pulmonary edema. Treatment had included IV administration of fluids, administration of sodium bicarbonate solution IV, oxygen insufflation, and nasotracheal intubation. The fourth horse was euthanatized within 8 hours of admission because of poor prognosis and lack of improvement in alertness and ataxia in response to treatment. Fluids, dopamine, furosemide, and ceftiofur had been administered. Minimal urine had been produced, and neurologic signs had worsened. Horse 5 died within 36 hours of admission after treatment by IV administration of fluids, and furosemide failed to induce urine production. This horse also had worsening of encephalopathic signs during this time.

Postmortem examination was performed on 4 horses; the owner of 1 horse would not allow a necropsy to be performed. Renal abnormalities varied but were characteristic of chronic renal disease. Kidneys were small and nodular on gross examination, with cortical atrophy and replacement of cortical tissue by areas of fibrosis. Dilatation of the renal pelvises was evident in 1 horse. Calculi were found in the renal pelvises of 2 other horses.

Microscopic changes in kidney sections included severe, diffuse, cortical, and medullary interstitial fibrosis; substantial tubular ectasia with protein casts, mineralization, degeneration, and necrosis; and multifocal accumulations of interstitial lymphocytes and plasma cells. Microscopic glomerular lesions varied from none to moderate thickening of Bowman's capsules to glomerulosclerosis. Final renal pathologic diagnoses from individual horses included diffuse chronic-supparative interstitial nephritis with diffuse chronic glomerular sclerosis, bilateral renal dysplasia with severe cortical and medullary fibrosis, and severe diffuse chronic-supparative interstitial nephritis and nephrosis. Urolithiasis was identified in 2 horses. Two horses had histologic evidence of pyelonephritis.

All horses had clinicopathologic or histologic evidence of mild to moderate hepatic disease. One horse had serum activities of hepatic enzymes and total bilirubin concentration that were slightly above reference ranges as well as low albumin concentration. Histologic examination revealed moderate centrilobular hepatocellular hydropic degeneration. A second horse had serum GGT and **aspartate aminotransferase (AST)** activities that were slightly above reference ranges, whereas serum glucose, albumin, and total bilirubin concentrations were within reference ranges. Histologic examination revealed mild biliary hyperplasia. A third horse had a bile acid concentration that was slightly above reference range, whereas liver enzyme activities and total bilirubin, albumin, and glucose concentrations were within reference ranges. Mild to moderate degenerative hepatopathy was found microscopically. A fourth horse had GGT and sorbitol dehydrogenase activities that were substantially above reference ranges, total bilirubin concentration slightly above reference range, and serum activity of AST that was moderately above reference range; hypoglycemia and hypoalbuminemia were not detected. A necropsy

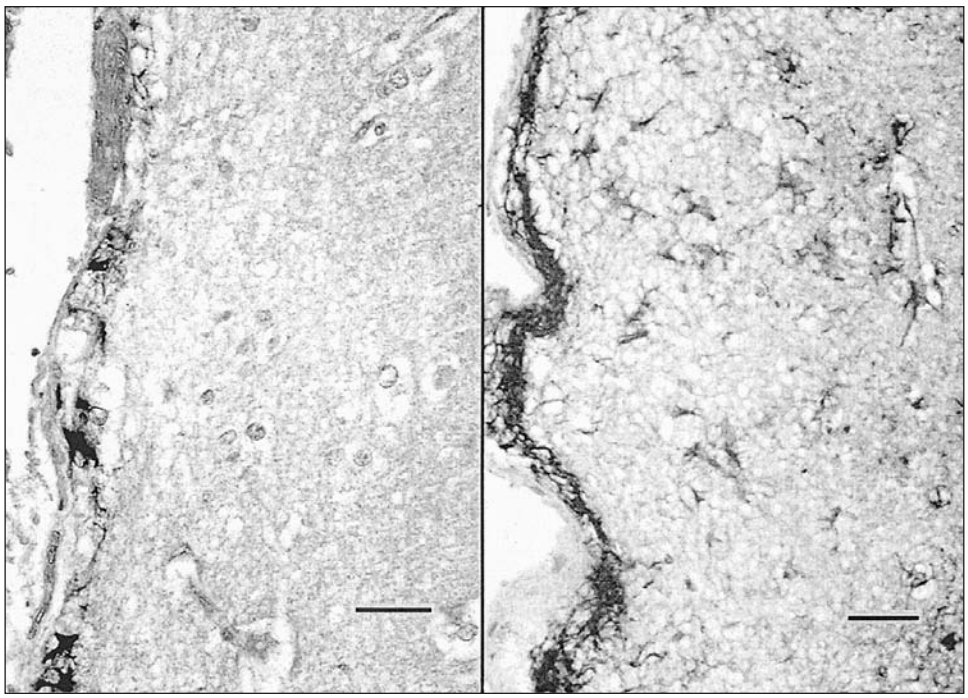

Figure 2—Photomicrographs of a section of cerebral cortex (including the edge of a sulcus and the pia mater) from a horse with putative uremic encephalopathy (left) and from a healthy control horse (right). Notice substantially less intense immunohistochemical staining of glial fibrillary acidic protein in the horse with putative uremic encephalopathy, compared with the control horse, especially along the glia limitans where gray matter meets the meningeal surface. Immunohistochemical stain; bar = 40 µm.

was not performed on this horse. The fifth horse had clinicopathologic abnormalities that may be present with liver disease but are not specific to the liver (AST, 2,072 U/L; serum ammonia concentration, 831 µg/dl). A necropsy was performed; neither gross nor histologic hepatic lesions were detected.

Gross lesions were not detected in the CNS of any of the 4 horses that were necropsied. Consistent histologic findings in the brains of all 4 horses with putative UE included substantial swelling of astrocytes, with increased nuclear diameter and expansion of the cytoplasm. Astrocytic nuclei had finely dispersed and peripheralized chromatin (**Fig 1**). Affected astrocytes were evident individually, in pairs, and in small clusters. Astrocytes in the control horses were smaller and had more prominently stained chromatin; enlarged astrocytes were uncommon and were evenly distributed in the gray and white matter. Astrocytic swelling in the brains of horses with putative UE was most evident in the cerebrocortical gray matter, caudate nucleus, and hippocampus. Fewer swollen astrocytes were evident in white matter tracts, midbrain, medulla oblongata, and cerebellum, and other substantial microscopic changes were not detected. Fluorescent antibody examination to identify rabies virus was performed on neural tissue from 2 horses; results were negative.

Mean ± SD astrocyte nuclear diameter for the 4 horses with putative UE was 10.9 ± 1.4 µm. Mean astrocyte nuclear diameter from comparable anatomic locations in the control horses was 7.2 ± 0.92 µm. Data for both groups were normally distributed; astrocyte nuclear diameter of horses with putative UE was significantly ($P < 0.001$) greater than that of control horses.

Immunohistochemical staining of the brains of 4 horses with putative UE revealed substantially less GFAP immunoreactivity than that of comparable sections of brain from control horses. Low staining was most conspicuous in the gray matter and glia limitans (**Fig 2**). Affected gray matter areas included cerebral cortex, basal ganglia, hippocampus, and cerebellum. Staining intensity of white matter was similar between groups. Slides from paraffin blocks of clinically normal horses, which had been stored for long periods, had GFAP immunoreactivity similar to that of unaffected control horses and greater than that of horses with putative UE. For both groups, staining scores were not distributed normally. Median values were 6.5 (range, 5 to 8) for horses with putative UE and 2.5 (range, 1 to 4) for control horses; horses with putative UE had significantly ($P = 0.029$) less GFAP immunoreactivity in brain tissue than did control horses.

Discussion

Encephalopathy secondary to renal failure has been reported in humans[1-3] and a variety of animal species[4-8] but remains poorly defined and rarely recognized in horses. In the 20-year retrospective study reported here, few (5/332) horses were identified with clinical evidence of UE, possibly because the syndrome has only recently been recognized in horses. It is also probable that subtle neurologic signs were not documented in all horses with renal disease, and, thus, those horses were not included in our study. Thirty-

eight horses with renal disease were eliminated from the study because of concomitant diseases such as colic, endotoxemia, severe hepatic disease, or neurologic disease, which potentially caused altered mentation or weakness. It is unclear in these horses to what degree UE may have contributed to these signs. Because UE is a clinical diagnosis made by excluding other causes of neurologic disease, case selection for this report was conservative.

The mild to moderate severity of liver disease in these 5 horses, without evidence of liver failure, suggested that liver disease did not solely cause the neurologic signs, although 2 horses may have had neurologic signs attributable to multiple causes. One horse had clinicopathologic findings suggestive of hepatic disease; because a postmortem examination was not performed, the degree to which hepatic dysfunction contributed to signs of encephalopathy could not be estimated. Another horse had high concentrations of serum ammonia and BUN attributable to renal failure or functional conversion of ammonia to urea by the liver. Increased serum ammonia concentrations were detected in a dog with renal failure without concomitant hepatic failure[10]; this is believed to result from suppression of normal urea production by the urea cycle under acidotic conditions. To promote nitrogenous waste excretion, healthy kidneys extract glutamine formed by amidation of glutamate in the liver. Enzymes act on glutamine to release ammonia, which is subsequently excreted into the urine. Diseased kidneys may not be able to excrete this ammonia, resulting in its accumulation in the serum. Additionally, hyperammonemia without liver dysfunction has been attributed to urinary stasis and urea-splitting organisms in humans.[11,12] Liver dysfunction was not a likely contributor to hyperammonemia in the horse with high concentrations of ammonia and BUN, because this horse did not have gross or microscopic liver lesions. In most instances, in horses, hyperammonemia resulting from liver dysfunction is attributed to serum hepatitis or chronic pyrrolizidine alkaloid poisoning,[13] which are associated with hepatic lesions. Idiopathic hyperammonemia,[14] urea poisoning, or enzyme deficiencies cannot be definitively excluded as possible contributors to hyperammonemia, and, therefore, encephalopathy in the horse with high ammonia and BUN concentrations.

Weight loss, clinicopathologic data, necropsy findings, and refractoriness to treatment supported a diagnosis of chronic or acute on chronic (rather than solely acute) renal failure in these 5 horses. Findings in these horses suggested that putative UE was associated with severe chronic renal failure. Although 4 of the 5 horses were < 10 years of age, evidence of developmental abnormalities (eg, renal agenesis, renal hypoplasia, or polycystic kidney disease) was detected in only 1 horse. It is possible that toxic or hemodynamic insults experienced when young contributed to chronic renal disease in these horses. Two horses were reported to have had acute onset of signs. This may have represented acute renal failure after chronic renal failure attributable to exhaustion of compensatory mechanisms. One horse had hyperglycemia and hematuria, which are uncharacteristic of acute renal failure. It is possible that hyperglycemia represented a stress response, because the horse had severe neurologic signs and required supplemental oxygen administration upon admission. Hematuria was likely secondary to urolithiasis detected at postmortem examination. In 1 horse, oxalate crystals were present throughout the kidney. Oxalate crystals likely represent decreased renal perfusion that results in crystal accumulation rather than primary oxalate-induced renal failure.

Clinically, renal failure in the horses reported here was characterized by azotemia and isosthenuria. Urinalysis was performed in 3 horses, whereas the diagnosis of renal failure in 2 horses was made by examining clinicopathologic data, clinical signs, and postmortem lesions. All of the abnormal biochemical values were attributable to renal failure, but none were considered specific with regard to UE. Clinicopathologic data such as results of urinalysis and concentrations of creatinine, BUN, and electrolytes would be most helpful in ruling out renal failure and UE.

Because all 5 horses in our study died or were euthanatized, conclusions regarding reversibility of signs associated with UE in horses could not be formulated. In horses with hepatic encephalopathy, severity of neurologic signs does not correspond to the degree of reversibility of the underlying disease.[15] Reversal of UE in humans with acute renal failure has been described.[16]

Conclusions could not be drawn from our study regarding location of renal lesions and their relationship with development or severity of neurologic signs. This is consistent with the lack of correlation between type of lesion and severity of CNS signs in animals with hepatoencephalopathy.[15]

Astrocytes have a critical role in development and maintenance of normal functions in the CNS.[17] Alzheimer type-II astrocytes have been described in humans, horses with idiopathic hyperammonemia,[14] and 1 horse with uremic encephalopathy[18] as having enlarged open-faced nuclei with peripheralization of chromatin and are typically associated with hyperammonemia and encephalopathy. Alzheimer type-II astrocytes fail to form large numbers of glial fibers and have small amounts of GFAP, compared with normal astrocytes.[19] Astrocytic morphologic features in the 4 horses with putative UE that were examined were consistent with some authors' descriptions of Alzheimer type-II astrocytes.[14,18,20,21] Decreased immunohistochemical staining of GFAP was also consistent with other reports of hyperammonemia.[14,18] Decreased immunohistochemical staining of GFAP in the horses examined here probably indicates that many astrocytes underwent metabolic changes associated with UE.

Many causes have been postulated for UE, including decreased cerebral metabolism and oxygen consumption,[22] inhibition of cerebral sodium-potassium ATPase,[23] increased concentration of parathyroid hormone,[24-27] accumulation of dialyzable metabolites,[28,29] and inhibition of the pentose-phosphate enzyme transketolase.[30,31] Of these causes, those involving accumulated metabolites and altered transketolase activity appear to be most valid. Researchers have failed to

detect strong correlation between clinical signs of the syndrome and any of the commonly assessed measurements of renal function.[3] The fact that dialysis moderates clinical signs suggests that the syndrome is attributable to accumulation of dialyzable metabolites.[28,29] Concentrations of 1 class of such metabolites, guanidinosuccinic acid and other guanidino compounds, are high in uremic patients because of decreased clearance and increased synthesis that results from accelerated protein metabolism. These compounds inhibit murine neuron response to γ-aminobutyric acid in cell culture and, thus, potentially contribute to the myoclonus and epilepsy detected in some patients with UE.[32] Guanidinosuccinic acid also inhibits excitatory impulses in the hippocampus in rats, potentially contributing to the alterations in cognitive function that are evident in patients with UE.[33]

The pentose-phosphate enzyme, transketolase, exists primarily in myelinated structures of the nervous system and may contribute to the health of myelin sheaths. This enzyme is inhibited by plasma, CSF, and dialysate fractions obtained from uremic patients.[30] The guanidino compound, guanidinosuccinic acid, also has an inhibitory effect on transketolase. This inhibition may promote loss of the myelin-protective effect, thus inducing demyelination with subsequent clinical signs.[31]

Although parathyroid hormone has been examined as a contributor to signs of encephalopathy in small animals,[24] it is felt that horses with renal failure do not develop secondary renal hyperparathyroidism. In a study of 6 horses with chronic renal failure and resulting hypercalcemia, evidence of primary hyperparathyroidism or pseudohyperparathyroidism could not be found,[34] suggesting that the role of the kidney in calcium homeostasis in horses is unique to this species.

The terms severe and chronic are used to describe the severity of renal disease in most cases of UE in various animal species.[4-8] Although acute renal disease or failure was included in our search criteria, signs of putative UE were not described in the medical records of horses with acute renal disease. On the basis of results of our retrospective study, one may conclude that evidence supportive of chronic renal failure such as ultrasonographic findings, clinicopathologic data, gross and histologic lesions, and pertinent historical details also support a diagnosis of UE in horses with neurologic signs. Uremic encephalopathy should be on the veterinary practitioner's list of differential diagnoses when examining any horse with neurologic signs that is moderately to severely azotemic and isosthenuric (ie, in renal failure). Presently, UE must remain a diagnosis of exclusion.

[a]Metamorph, version 4.0, Universal Imaging, Brandywine, Penn.
[b]Statview, version 5.0, SAS Institute Inc, Cary, NC.
[c]Ventana ES, Ventana Medical Systems, Tucson, Ariz.
[d]Cellmarque, Austin, Tex.

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