

# Seasonal pasture myopathy in horses in the midwestern United States: 14 cases (1998–2005)

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## ABBREVIATIONS

AM	Atypical myopathy
CK	Creatine kinase
NADH	Nicotinamide adenine dinucleotide
GC-MS	Gas chromatography coupled with mass spectrometry
AST	Aspartate transaminase

**Objective**—To determine clinical signs, diagnostic findings, tissue tremetone concentrations, and clinical outcome or postmortem findings in horses evaluated for acute severe nonexertional rhabdomyolysis initially attributed to white snakeroot toxicosis.

**Design**—Retrospective case series.

**Animals**—14 horses.

**Procedures**—Records of the University of Minnesota Veterinary Medical Center or Diagnostic Laboratory were searched from 1998 to 2005. Inclusion criteria included serum creatine kinase (CK) activity > 45,000 U/L, severe nonexertional myonecrosis of proximal postural muscles at necropsy, or signs of weakness without palpably firm muscles on physical examination. Vitamin E and selenium concentrations were measured in 6 horses; tremetone concentration was measured in 7.

**Results**—Clinical signs occurred during unfavorable weather conditions. Clinical signs of generalized weakness (n = 11 horses), muscle fasciculations (10), lethargy (6), and prolonged recumbency (4) were common. Serum CK activity ranged from 46,487 to 959,499 U/L (reference range, 82 to 449 U/L), and aspartate transaminase activity was > 1,500 U/L (reference range, 162 to 316 U/L). Two horses survived with aggressive antioxidant and fluid treatment. Postmortem examination revealed acute severe myonecrosis with lipid accumulation primarily in neck, proximal forelimb and hind limb, intercostal, and diaphragm muscles. Histopathologic signs of myocardial necrosis were detected in 7 horses. Vitamin E and selenium concentrations were within reference limits. Tremetone was not detected in liver or urine samples.

**Conclusions and Clinical Relevance**—Cases of rhabdomyolysis have been attributed to white snakeroot toxicosis; however, tremetone was not detected in any horses. Similarities exist between cases of seasonal pasture myopathy and cases of atypical myopathy in Europe. (*J Am Vet Med Assoc* 2006;229:1134–1141)

in horses that is not associated with exercise has been attributed to vitamin E or selenium deficiency,<sup>1,2</sup> polysaccharide storage myopathy,<sup>2,4</sup> postanesthetic myopathy,<sup>2,5</sup> concurrent infection with *Streptococcus equi*<sup>2,6,7</sup> or *Salmonella* serovar Infantum,<sup>8</sup> and plant toxicities.<sup>9,10</sup> In Europe, outbreaks of severe nonexertional rhabdomyolysis in pastured horses have been termed atypical myoglobinuria or AM.<sup>11</sup> Atypical myopathy is commonly reported to occur in autumn a few days after inclement weather. Clinical signs of AM include sudden onset of stiffness progressing to recumbency with markedly increased CK activity and myoglobinuria.<sup>11–14</sup> Atypical myopathy most often results in death, and severe acute myonecrosis is detected in the postural skeletal muscles, respiratory muscles, and myocardium during postmortem examination.<sup>11</sup> Similar clinical and pathologic findings have been described in pastured horses in the United States. These findings have been attributed to tremetone toxicosis from ingestion of the white snakeroot plant (*Eupatorium rugosum*).<sup>15,16a</sup> The purpose of the study reported here was to review the clinical signs, diagnostic findings, tissue tremetone concentrations, and clinical outcome or postmortem findings of horses in Minnesota that were evaluated for acute severe nonexertional rhabdomyolysis initially attributed to white snakeroot toxicosis. Results indicated many similarities between AM in Europe and cases of pasture myopathy that may have been previously attributed to white snakeroot toxicosis in the United States.

## Criteria for Selection of Cases

A computer search of the medical record database was performed at the University of Minnesota Veterinary Medical Center and the University of Minnesota Diagnostic Laboratory from January 1998 to November 2005 to identify horses with nonexertional rhabdomyolysis suspected to have been caused by white snakeroot toxicosis. Initial suspicion of white snakeroot toxicity was based on clinical signs and postmortem findings, which included acute severe rhabdomyolysis, palor or hemorrhage of postural and respiratory skeletal muscles, and palor or hemorrhage in the

**D**etermining the etiology of and successfully treating acute severe rhabdomyolysis in horses are particularly challenging. In the United States, rhabdomyolysis

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myocardium. Inclusion criteria included serum CK activity > 45,000 U/L, severe nonexertional myonecrosis of proximal postural muscles at necropsy, or signs of weakness without palpably firm muscles on physical examination. The information obtained included date of admission, signalment, initial clinical signs, duration of clinical signs, housing, diet, vaccination history, physical examination findings, clinicopathologic findings (when available), diagnostic test results, treatment, and disease progression. Additional data obtained from the veterinary diagnostic laboratory, where all necropsies were performed, included date of euthanasia or death and gross and histopathologic findings.

## Procedures

**Muscle histochemistry**—Percutaneous needle biopsy specimens of the gluteal and sacrocaudalis dorsalis muscles were obtained from 1 horse. Muscle specimens (heart, diaphragm, semimembranosus muscles, and iliopsoas muscles) obtained at necropsy from 3 horses were frozen in isopentane chilled in liquid nitrogen, within 2 hours of euthanasia. Ten 10- $\mu$ m sections were stained with H&E, periodic acid-Schiff, Gomori trichrome, and oil red O stain for NADH tetrazolium reductase reaction. Semimembranosus muscle biopsy specimens from healthy horses that were processed immediately were used as control specimens. In addition, control specimens of heart, iliopsoas, and semimembranosus muscles that were kept chilled and processed within 24 hours were obtained from horses that were euthanized because of polysaccharide storage myopathy. Similar samples, including adductor muscles, were also obtained and processed within 2 hours from a 2-year-old horse euthanized because of cervical vertebral malformation.

**Pasture inspection**—When possible, within 1 week from initial evaluation of horses, pastures had been examined by a veterinarian certified by the American Board of Veterinary Toxicology or the referring equine veterinarian familiar with the appearance of the white snakeroot plant. Pastures of 5 horses were not inspected.

**Weather conditions**—A computer search of the weather history database was performed by use of the Farmer's Almanac<sup>17</sup> for the dates of hospital admission or the dates of death or euthanasia. Weather conditions examined each day for 7 days prior to admission included mean temperature; mean precipitation; wind velocity; and occurrences of rain, snow, thunder, fog, and hail. Mean monthly temperatures for Minneapolis-Saint Paul were obtained for the past 30 years.

**Vitamin E and selenium analysis**—Serum vitamin E and whole-blood selenium concentrations were measured in 1 horse. Hepatic vitamin E and selenium concentrations were measured in 5 horses.

**Ionophore analysis**—A sample of feed fed to 1 horse was tested for ionophores via thin-layer chromatography with colorimetric detection.

**Tremetone analysis**—Liver tissue (30 g) was collected from 6 horses during necropsy and stored at

–20°C until analysis. In 1 horse that survived, 240 mL of urine was collected via catheterization and shipped on ice packs until analyzed. All samples were shipped on ice to the University of Illinois Veterinary Diagnostic Laboratory and analyzed for tremetone concentration by use of GC-MS.<sup>b</sup>

## Results

Fourteen horses suspected of having white snakeroot toxicosis were identified in the databases. Suspicion of white snakeroot toxicosis was based on clinical signs (n = 2 horses) or necropsy findings (12), which included acute severe rhabdomyolysis (14), gross palor (6), or hemorrhage (3) of skeletal muscle; gross palor or hemorrhage of myocardial muscle (6); and identification of white snakeroot plants in the environment (3).

**Signalment**—Nine horses were alive at the time of initial evaluation at the veterinary medical center, 1 horse was treated at a local veterinary clinic but was later brought to the veterinary diagnostic laboratory, and 4 horses were brought to the veterinary diagnostic laboratory for postmortem examination. Breeds affected included Morgan (n = 3), Quarter Horse (3), Welsh pony (1), Norwegian Fjord (1), Thoroughbred (1), Tennessee Walking Horse (1), Saddlebred (1), and various mixed-breed horses (3). Ages of horses ranged from 1 to 22 years (mean, 6  $\pm$  5.8 years) and included 7 geldings and 7 mares.

**History**—Vaccination history was reported for 10 horses. In those horses, vaccination status for Eastern and Western equine encephalitis, tetanus, influenza, and equine rhinopneumonitis was adequate.

Nine horses had also been vaccinated against West Nile virus, and 6 had been vaccinated against rabies virus.

Diet and housing information was available for 13 of 14 horses. Twelve horses were housed completely on pasture, whereas 1 horse had access to pasture for 14 hours during the day and was stabled at night. Eight horses were fed pasture grass with hay but no supplemental grain, and 5 horses were fed pasture grass with hay and a moderate amount of supplemental grain (1 to 3 kg [2.2 to 6.6 lb] of sweet feed or rolled oats daily).

Information regarding other affected horses on the same property was available for 13 horses. On 1 farm, rhabdomyolysis had been diagnosed in 2 horses concurrently in the fall and in a third horse during a cold week in the spring. No problems were detected in any other horses from the same pasture or elsewhere on that farm. On a farm where 1 affected horse was housed, 1 other horse was also affected; however, no follow-up information was available for that horse. Five horses were maintained on a farm on which 1 affected horse was housed with 3 horses that were clinically normal. On that farm, 1 horse had died from unspecified causes a week before clinical signs were detected in the affected horse. On another farm, 1 affected horse was housed with 2 other horses that remained unaffected; serum CK activity in those 2 horses was within reference range. On that farm, a horse with similar clinical signs had been reported by the owner in 1993, and the postmortem report for that

horse indicated that it had severe rhabdomyolysis. Other affected horses were housed individually, or no other horses with similar clinical signs were reported on the same farm.

**Pasture inspection**—Pasture for 9 horses was inspected. Of the pastures inspected, toxic plants including white snakeroot were not identified in the pastures of 6 horses and white snakeroot plants were detected in pastures of 3 horses. On 1 farm, 2 affected horses shared a pasture in which white snakeroot was detected adjacent to a line of trees in a partially shaded area. The plants did not appear to have been grazed on. Another affected horse was housed on the same farm in a separate pasture; however, no evidence of white snakeroot or other toxic plants was detected in this separate pasture. On 1 farm, white snakeroot was detected in the pasture in which 1 affected horse was housed, with some evidence of consumption by horses. There had been a history of white snakeroot growth on the farm where another affected horse was housed; however, the plant was not detected in the pasture or hay when examined.

**Weather conditions**—Thirteen horses were initially evaluated from September to November, and 1 horse was evaluated during a particularly wet, cool May (mean temperature, 54°F). Rainfall (mean  $\pm$  SD precipitation, 0.07  $\pm$  0.8 inches) occurred 1 to 3 days prior to admission of 12 horses, and for 4 horses, thunderstorms were noted 1 to 3 days prior to admission. Of the 13 horses that were evaluated in the fall, the mean temperature 1 week prior to evaluation was higher ( $n = 8$  horses; mean  $\pm$  SD, 51°  $\pm$  8.7°F; difference, 14°  $\pm$  5.7°F), approximately equal (3;  $< 5^\circ\text{F}$  difference; mean  $\pm$  SD, 45°  $\pm$  11°F; difference, 1°  $\pm$  2°F), or lower (2; mean  $\pm$  SD, 48°  $\pm$  10°F; difference, 6.5°  $\pm$  2°F) than the 30-year mean temperature for Minneapolis-Saint Paul during those months (mean temperature, 44°  $\pm$  12°F). A decrease in the mean temperature of  $\geq 13^\circ\text{F}$  during the 7 days prior to admission was noted for 6 horses. When comparing the dates of admission with the dates of the first snowfall recorded for the year, 4 horses were evaluated 2 to 4 weeks prior to the first snowfall, 2 horses were evaluated 2 to 3 days after the first snowfall, and the remaining horses were evaluated 4 days to 6 weeks after the first snowfall.

**Clinical signs**—Initial clinical signs were described for all 14 horses. Clinical signs had an acute onset (median, 16 hours; range, 4 hours to 5 days) in most horses before evaluation by a veterinarian. Clinical signs included pigmenturia ( $n = 12$  horses), generalized weakness (11), muscle fasciculations (10), lethargy (6), prolonged recumbency (4), signs of colic (4), and muscle stiffness (2). Two horses also had esophageal obstruction. One horse had only mild muscle fasciculations; however, the owner was concerned because the horse's pasture mate had died 1 day earlier; pasture myopathy was suspected in that horse.

**Horses evaluated for postmortem examination**—Serum CK and AST activities were available from referring veterinarians for 2 of the 4 horses that were eval-

uated for postmortem examination. In 1 horse, the CK activity was 466,720 U/L (reference range, 82 to 449 U/L), whereas in the other horse, the CK activity was reported as  $> 2,036$  U/L but was not diluted to an actual value. Serum AST activities were 13,160 and 6,263 U/L (reference range, 162 to 316 U/L), respectively.

**Horses admitted to a veterinary clinic**—Nine horses were examined at the veterinary medical center, and 1 horse was examined at a local veterinary clinic. Three horses were recumbent in the trailer but stood with encouragement, and 1 recumbent horse required IV administration of fluids prior to standing and walking off the trailer. All horses had dull mentation and signs of depression and were 5% to 10% dehydrated. Rectal temperature was considered normal (37° to 38.5°C [99° to 101.3°F]) in 8 horses or decreased ( $< 36.7^\circ\text{C}$  [98°F]) in 2 horses. Tachycardia ranging from 52 to 120 beats/min was detected in 8 horses. The respiratory rate was considered normal (10 to 16 breaths/min) in 7 horses and increased (40 breaths/min) in 3 horses. Cardiac arrhythmias or murmurs were not detected in any of the examined horses. Five horses had a vigorous appetite, whereas 5 horses were anorexic, of which 3 had signs of colic and 2 had esophageal impactions. A rectal examination was performed on 5 horses; no notable findings were detected, with the exception of 1 horse in which a gas-distended colon was palpated at the pelvic inlet. Pigmenturia was detected in 9 horses.

On admission, muscle fasciculations were detected in 9 horses. Muscle fasciculations were localized to more than 1 site in most horses and included the triceps muscles ( $n = 9$  horses), hindquarters ( $n = 5$  horses; psoas major, gluteal, rectus femoris, gracilis, semimembranosus, and semitendinosus muscles), flank (2), muzzle (2), and neck (1). On palpation, muscles were pliable in 9 horses and firm in 1 horse, and palpation of muscles did not elicit signs of pain. Muscle atrophy was not detected in any horses. A complete neurologic evaluation was performed in 9 of 10 horses; except for dysphagia attributable to an esophageal obstruction in 2 horses, no abnormalities were detected.

In 9 horses, the Hct was  $> 45\%$  (reference range, 27 to 43%), and in 5 horses, the total plasma protein concentration was  $> 8$  g/dL (reference range, 6.1 to 7.9 g/dL). In 6 horses, total leukocyte counts were within reference ranges (reference range, 4,600 to 11,600 cells/ $\mu\text{L}$ ). Leukocytosis (range, 12,000 to 16,600 cells/ $\mu\text{L}$ ) was reported in 4 horses. In 5 horses, the differential WBC count was considered normal, 4 horses had a mature neutrophilia (range, 8,550 to 11,320 cells/ $\mu\text{L}$ ; reference range, 1,500 to 8,500 cells/ $\mu\text{L}$ ), and 1 horse had a regenerative left shift (664 band neutrophils/ $\mu\text{L}$ ; reference range, 0 to 0.1 band neutrophils/ $\mu\text{L}$ ). Plasma fibrinogen concentration was measured in 7 horses and was considered normal ( $< 0.4$  g/dL) in 5 horses and was slightly high (0.5 g/dL) in 2 horses.

Serum CK (range, 46,487 to 959,499 U/L; mean, 240,792 U/L; reference range, 82 to 449 U/L) and AST (range, 1,500 to 27,395 U/L; mean, 10,580; reference range, 162 to 316 U/L) activities were high in all hors-

es admitted to the hospital. Other biochemical abnormalities included high activities of serum alkaline phosphatase (n = 9 horses; range, 164 to 675 U/L; reference range, 48 to 148 U/L), sorbitol dehydrogenase (6; range, 9 to 72 U/L; reference range, 1 to 7 U/L), and  $\gamma$ -glutamyltransferase (5; range, 19 to 41 U/L; reference range, 9 to 17 U/L) and high concentrations of total bilirubin (7; range, 2.3 to 4.9 mg/dL; reference range, 0.3 to 1.8 mg/dL) and glucose (8; range, 126 to 418 mg/dL; reference range, 75 to 116 mg/dL). In 6 horses, the serum concentration of bicarbonate was low (range, 15 to 24 mM; reference range, 25 to 31 mM). Electrolyte abnormalities included low total serum calcium concentration (n = 8 horses; range, 5.8 to 10.3 mg/dL; reference range, 10.4 to 12.9 mg/dL), hyperphosphatemia (8; range, 4.6 to 12.5 mg/dL; reference range, 2.7 to 4.4 mg/dL), hyperkalemia (1; 5.7 mmol/L; reference range, 3.6 to 5.1 mmol/L), hyponatremia (2; range, 122 to 126 mmol/L; reference range, 130 to 140 mmol/L), and hypochloremia (4; range, 79 to 93 mmol/L; reference range, 95 to 103 mmol/L). Blood urea nitrogen and creatinine concentrations were within reference ranges in 5 horses (range, 13 to 23 mg/dL and 0.7 to 1.7 mg/dL, respectively) and were moderately high in 5 horses (range, 26 to 50 mg/dL and 1.9 to 3.8 mg/dL, respectively).

In all horses, urine was dark brown and results of a dipstick analysis were positive for occult blood (3 to 4+/5) and protein (2 to 4+/5). Urine from 8 horses was centrifuged, and the abnormal pigment remained in the supernatant. In 1 horse, RBCs were detected in the abnormally colored supernatant. Urine specific gravity was measured in 5 horses and ranged from 1.006 to 1.038 (mean, 1.029; reference range, 1.020 to 1.050). Glucose (3+/5; plasma glucose concentration, 285 mg/dL) was detected in 1 horse. Myoglobinuria was confirmed by electrophoresis in 1 horse.

Echocardiography performed in 3 horses revealed no notable abnormalities, and fractional shortening was considered normal, ranging from 36% to 38%. Troponin-1 concentrations were measured in 2 horses and were < 0.07 and 0.09 ng/mL, respectively, both of which were within the reference range reported for horses.<sup>c,d</sup>

Treatment included IV administration of fluids (n = 9 horses) and administration of anti-inflammatory drugs such as flunixin meglumine and phenylbutazone (6), antioxidants including vitamin E and selenium (5), dimethyl sulfoxide (4), and vitamin C (1). Sedation and analgesia were maintained with detomidine and butorphanol (n = 5 horses) or acepromazine (2). Dantrolene sodium was administered in 3 horses. Other treatments included dexamethasone (n = 1 horse), activated charcoal (1), and potassium penicillin and gentamicin (1). An exploratory celiotomy was performed in 1 horse because of unrelenting signs of colic and abnormal findings detected during rectal examination. Mild gas distension was detected during surgery; however, no other notable gastrointestinal tract abnormalities were detected.

Two horses that were evaluated within 4 hours of developing clinical signs survived to discharge (1 to 3 days after evaluation). One of these horses was treated

with phenylbutazone (2.2 mg/kg [1 mg/lb], PO, q 12 h) and vitamin E (5,000 units, PO, q 24 h). Serum CK activity in that horse decreased during a period of 5 days (serum CK activity at admission, 46,487 U/L; 1 day after admission, 29,842 U/L; and 5 days after admission, 1,426 U/L). A follow-up examination performed in that horse 6 months after discharge revealed no residual clinical signs.

The other horse responded to treatment with vitamin E and selenium<sup>c</sup> (0.02 mL/kg [0.01 mL/lb], IM) given once followed by administration of vitamin E (5,000 units, PO q 24 h), vitamin C (5,000 mg in 5 L of lactated Ringer's solution, IV, q 24 h, for over 12 hours), 2.5% solution of dimethyl sulfoxide in lactated Ringer's solution (IV, q 24 h, for 3 days for over 4 hours), flunixin meglumine (1.1 mg/kg [0.5 mg/lb], IV, q 12 h), and balanced polyionic fluids (2.2 mg/kg/h [1.1 mg/lb/h], IV). Serum CK activity in this horse increased from 256,103 U/L at admission to 264,359 U/L 1 day after admission, then subsequently decreased to 31,524 U/L 3 days after admission. Biopsy specimens of sacrocaudalis and gluteal muscles were evaluated with H&E, periodic acid-Schiff, and oil red O stains and NADH tetrazolium reductase. Except for a mild increase in intracellular lipid staining in the gluteal muscle biopsy specimen, no histopathologic abnormalities were detected. No residual clinical signs were detected during a follow-up examination of the horse performed 2 months after discharge.

Rapid clinical deterioration was detected in the remaining 8 horses within hours of evaluation. One horse died within 7 hours of evaluation, and 7 were euthanized (mean  $\pm$  SD time after evaluation, 19  $\pm$  16 hours).

**Postmortem findings**—A complete postmortem examination was performed on 12 horses. Moderate to marked subcutaneous edema was detected along the neck and sternum and between the hind limbs of 8 horses. The edema extended between the fascial muscle planes of the major weight-bearing muscles. Three horses did not have grossly visible skeletal muscle lesions. Skeletal muscles had moderate to marked palor in 6 horses and hemorrhage in 3 horses (Figure 1).

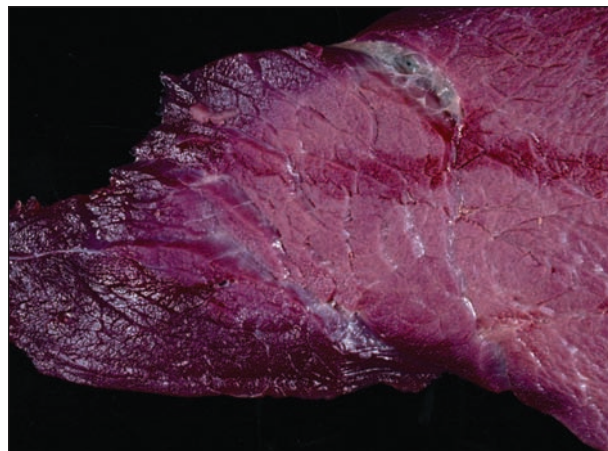


Figure 1—Photograph of a cut section of the gluteal muscle from a horse with seasonal pasture myopathy; the muscle was obtained immediately after euthanasia. Notice marked widespread irregular areas of palor.

The myocardium had diffuse or multifocal pale areas with ecchymoses, full-thickness white streaks extending through the myocardium of the ventricles, or focal areas of hemorrhage. Gross cardiac lesions were not detected in 6 horses. In 2 horses, the kidneys were soft, pale, and friable with an indistinct corticomedullary junction. In 5 horses, the urinary bladder contained dark-brown urine.

A large amount of yellow to brown watery fluid was detected in the pericardium of 5 horses, the thoracic cavity in 3 horses, and the peritoneal cavity in 2 horses. Lungs were diffusely congested, wet, and heavy, and foam was reported in the trachea and bronchi of 3 horses. Four horses had linear gastric ulcerations. Other gastrointestinal tract lesions included an edematous and thick cecal wall mucosa (n = 1 horse), esophageal impaction (1), and hemorrhage on the jejunal serosa (1) or on the serosa of the right dorsal colon (1).

Acute severe muscular degeneration and necrosis were detected in all horses. The specific muscle groups affected were identified in 11 horses and included the caudal aspect of the neck and shoulder (trapezius, brachialis, rhomboideus, subscapularis, triceps, and pectoralis muscles), hindquarters (psoas major, gluteal, rectus femoris, gracilis, semimembranosus, and semitendinosus muscles), back (longissimus dorsi muscle), intercostal muscles, tongue, and diaphragm. Zenker's degeneration, characterized by loss of cross-striations, fiber swelling, hypereosinophilia of the sarcoplasm, hyaline fragmentation of the sarcoplasm of individual muscle fibers, and pyknotic nuclei, was detected in the skeletal muscle fibers (Figure 2). Macrophage infiltrates varied from minimal (n = 6 horses) to extensive (2). Mild to moderate infiltration of neutrophils along the skeletal muscle fibers and mineralization of skeletal muscles were detected in 1 horse. Periodic acid-Schiff staining with and without amylase digestion was performed on skeletal muscles from all horses. Evidence of slightly increased amounts of amylase-resistant polysaccharide was detected in a few muscle fibers from 1 horse. Results of oil red O staining of frozen samples of skeletal muscle fibers from 4 horses indicated marked accumulation of intra-

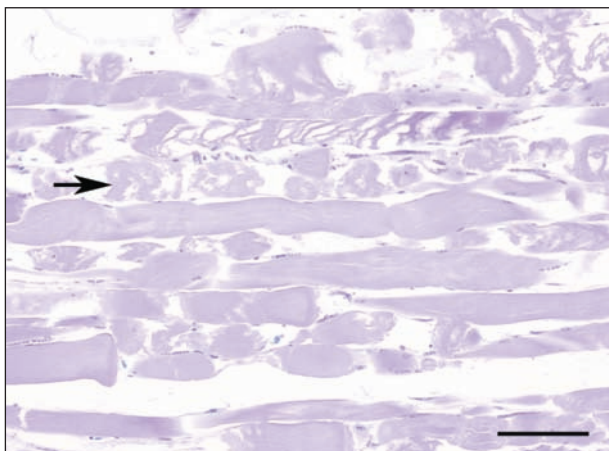


Figure 2—Photomicrograph of a longitudinal section of skeletal muscle fixed in neutral-buffered 10% formalin obtained from a horse with seasonal pasture myopathy. Notice acute necrosis and hyaline degeneration (arrow) in multiple myofibers with fragmentation of the sarcoplasm. H&E stain; bar = 100  $\mu$ m.

and extracellular lipid (Figure 3). Increased lipid storage was apparent in fibers that stained darkly for NADH tetrazolium reductase reaction (highly oxidative fibers) as well as in necrotic muscle fibers. Sections of skeletal

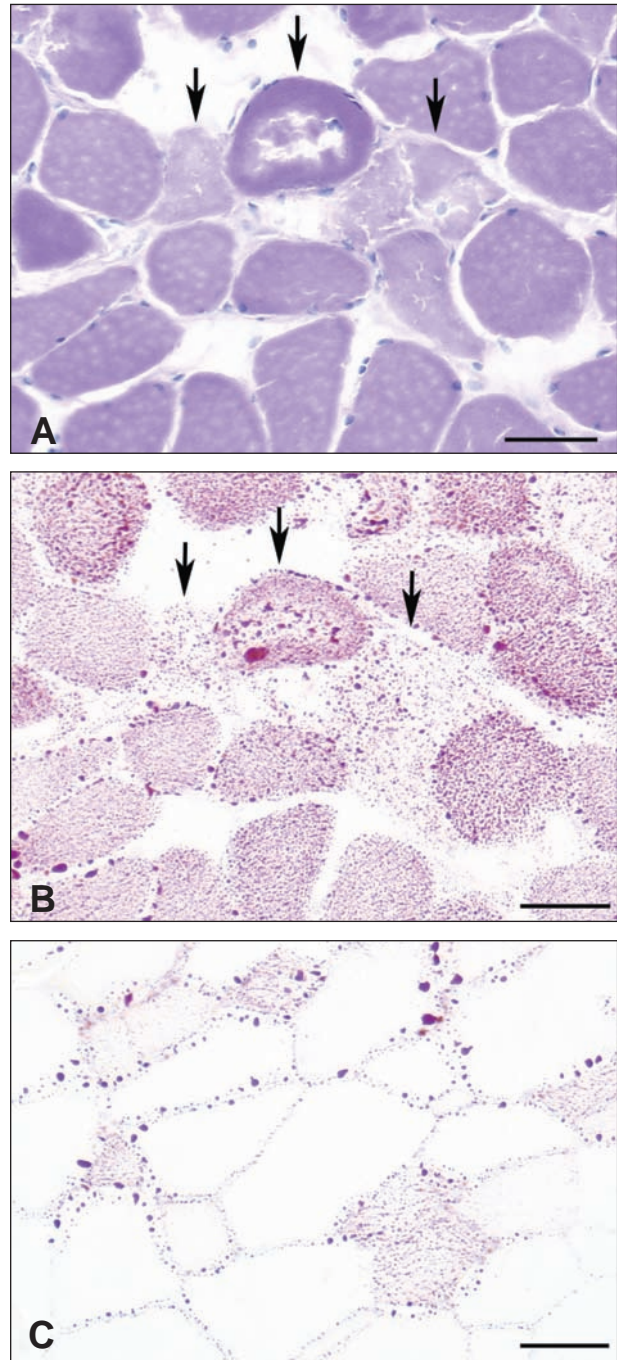


Figure 3—Photomicrographs of serial cross sections of the iliopsoas muscle near its insertion from a horse with seasonal pasture myopathy (A and B) obtained within 2 hours of euthanasia. Panels A and B—Three fibers are undergoing acute myonecrosis (arrows). The intracellular lipid content of myofibers is markedly increased, compared with that in control tissue from a 2-year-old horse euthanized because of cervical vertebral malformation. Sections are stained with H&E (A) and oil red O (B); bar = 50  $\mu$ m. Panel C—Only a few fibers in control tissue have intracellular lipid staining and some irregularly distributed endomysial lipid droplets. Prominent lipid accumulation is primarily detected in type 1 fibers. Oil red O stain; bar = 50  $\mu$ m.

muscle fibers from all control horses had a few fibers with visible lipid staining and a few scattered areas of extracellular lipid accumulation.

Moderate to severe myocardial degeneration and necrosis without inflammatory infiltrates were detected in 6 of the 12 horses, and mild myocardial degeneration was detected in 1 horse (Figure 4). Acute, focally extensive subendocardial hematomas without evidence of myocardial degeneration were detected in 3 horses. No notable abnormalities were detected during histopathologic examination of cardiac tissue from 2 horses. There was extensive lipid staining in all of the cardiac myocytes in frozen sections from 2 horses.

Mild to moderate acute tubular necrosis was evident in most horses, and granular pink to red proteinaceous casts were detected in the tubular lumina of the renal medulla (9 horses). Moderate to marked pulmonary congestion was evident in the lungs from 8 of the 12 horses evaluated. In 4 horses, the liver had acute portal congestion. Degeneration and necrosis of the urinary bladder wall with submucosal edema were detected in 1 horse, and acute esophagitis was detected in another horse.

**Vitamin E and selenium concentrations**—Serum concentrations of vitamin E and concentrations of selenium in whole blood were within or greater than the reference range in 1 horse (3.83  $\mu\text{g}/\text{mL}$  [reference range, 2 to 4  $\mu\text{g}/\text{mL}$ ] and 337 ng/mL [reference range, 160 to 275 ng/mL], respectively). Hepatic vitamin E and selenium concentrations analyzed in 5 horses were within the reference range (20 to 40  $\mu\text{g}/\text{g}$  of dry wt and 0.7 to 2.0  $\mu\text{g}/\text{g}$  of dry wt, respectively) in 4 horses, whereas the hepatic vitamin E concentration was marginal in 1 horse (15.66  $\mu\text{g}/\text{g}$  of dry wt).

**Ionophore analysis**—Feed given to 1 horse was tested for ionophores, and results were negative.

**Tremetone analysis**—Concentrations of tremetone or its metabolites were not detected in liver samples from 6 horses and in urine submitted antemortem from 1 horse.

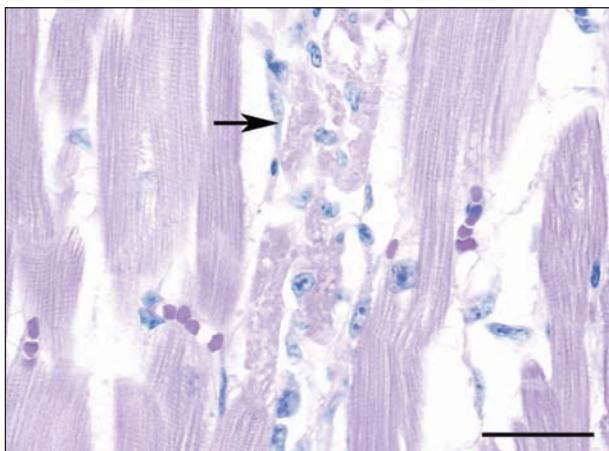


Figure 4—Photomicrograph of a longitudinal section of the myocardium from a horse with seasonal pasture myopathy. Notice hyaline degeneration and necrosis with fragmentation of the sarcoplasm (arrow) in the central myocyte that is also infiltrated by a few macrophages. H&E stain; bar = 30  $\mu\text{m}$ .

## Discussion

In the study reported here, the consistent demographic, clinical, postmortem, and histopathologic findings among horses suggested that there may be a seasonal pasture myopathy in horses in Minnesota. In our study, adult horses developed acute clinical signs of rhabdomyolysis and 7 horses developed myocardial degeneration while on pastures without snow cover when minimum daily temperatures were from 29° to 56°F and weather was often inclement. Potential causes for this type of myopathy include nutritional myodegeneration, ionophore toxicosis, plant toxicosis, and atypical myopathy. However, the cause of these findings in all horses may not have been the same.

Although cases of nutritional myodegeneration, attributable to selenium and vitamin E deficiency, most commonly develop in animals < 2 months old,<sup>1,18</sup> there are infrequent reports in adults. Clinical signs of maxillary myositis or polymyositis characterized by dystrophic mineralization have been reported in adult horses in association with vitamin E and selenium deficiencies.<sup>13,19</sup> In the study reported here, nutritional myodegeneration appears as an unlikely cause of clinical signs because adequate hepatic vitamin E and selenium concentrations were measured in 5 horses with pasture myopathy. Furthermore, dystrophic mineralization, which can be seen in horses with nutritional myodegeneration,<sup>19</sup> was not a consistent finding in all horses. Ionophore toxicosis, specifically monensin toxicosis, is an important differential diagnosis for horses with cardiac and skeletal muscle necrosis. Clinical signs of toxicosis in numerous horses on a premise are commonly attributable to feeding grain that has been accidentally contaminated with monensin during grain processing or transport.<sup>2</sup> Clinical signs of monensin toxicosis are dominated by cardiac failure and consist of a rapid, irregular heart rhythm or muffled heart sounds as well as partial to complete anorexia.<sup>2,20</sup> The heart, diaphragm, and oxidative skeletal muscles are the primary targets of monensin. Lesions in the myocardium are pronounced and characterized by pale myofibrils, loss of fiber striation, and multifocal vacuolar degeneration.<sup>20</sup> In our study, horses primarily had skeletal muscle weakness, did not have cardiac arrhythmias, and often had an excellent appetite. Horses with ionophore toxicosis often have myocardial changes that are detectable echocardiographically, which include decreased myocardial contractility and decreased shortening fractions of as low as 7%.<sup>21</sup> In the study reported here, results of echocardiography performed in 3 horses were considered normal. Feed fed to 1 horse was tested for ionophores; results were negative. Furthermore, only 3 of the 6 horses in which gross myocardial lesions were detected were fed grain; no other horses fed grain were concurrently affected on farms on which those 3 horses were housed. Thus, we postulate that exposure to monensin did not occur, although analysis of monensin concentrations in the feed was not performed in most of the cases of pasture myopathy.

Plants associated with myonecrosis include *Senna occidentalis* (*Cassia occidentalis* or Coffee senna), *Senna obtusifolia* (*Cassia obtusifolia* or Sicklepod), *Thermopsis montana* (Golden banner), *Karwinskia humboldtiana* (Coyotillo), *Vicia villosa* (Hairy vetch), *Cestrum diurnum* (Day blooming jasmine), as well as those plants contain-

ing cardiac glycosides and tremetone.<sup>22</sup> Of all of these plants, white snakeroot (*E rugosum*) was the only one that was detected in some of the pastures in our study. The seasonal occurrence of the myopathy in our study as well as the acute clinical signs of muscle fasciculations, weakness, esophageal obstruction, colic, and pigmenturia were consistent with white snakeroot toxicosis.<sup>9,15,16,23-28</sup> In addition, the specific skeletal muscles affected by white snakeroot<sup>4</sup> were similar to those affected in horses described herein. However, in addition to the gluteal, pectoral, pharyngeal, and temporal muscles affected by white snakeroot toxicosis, horses in the study reported here had prominent involvement of postural and respiratory muscles. Furthermore, signs of myocardial arrhythmias and myocardial necrosis appear to be more consistently associated with white snakeroot toxicosis, compared with the myopathy described in our study.<sup>26,27,29</sup> Signs that were not observed in our study but are reported for white snakeroot toxicosis include third-degree atrioventricular block and ST segment depression,<sup>29</sup> increased atrial rate, varying QRS complexes, and ventricular premature beats.<sup>26</sup> Myocardial lesions detected with white snakeroot toxicosis include mineralization of the myocardium and extensive infiltration of mononuclear cells,<sup>26</sup> both of which were not detected in horses in our study. Thus, although some of the epidemiologic and clinical findings resembled those detected with white snakeroot toxicosis, other findings were not compatible with this diagnosis.

The toxic dose of white snakeroot varies from 0.5% to 10% body weight when ingested for as long as 3 weeks,<sup>9,23,28</sup> and toxicity appears to require microsomal activation through the cytochrome P450 system.<sup>30-32</sup> The toxicity of white snakeroot plants can be highly variable, with toxicity detected with *E rugosum* of 1 variety and not detected in another variety collected from the same location.<sup>33</sup> In the study reported here, there were only 2 farms on which white snakeroot plants were identified in amounts that would likely induce clinical signs.<sup>1</sup> It is possible that other plants containing the toxin tremetone were consumed by horses in our study; however, they were not identified in the pastures inspected. To further investigate this possibility, tremetone as well as dehydrotremetone, dihydrotremetone, and hydroxytremetone were assayed in liver samples of 6 affected horses and in a urine sample of 1 affected horse by GC-MS. In a study<sup>16</sup> of horses in which white snakeroot toxicosis was suspected, tremetone was not detected in blood, urine, liver, or kidney samples nor in stomach or cecal contents. However, use of recently developed GC-MS techniques at the Illinois Veterinary Diagnostic Laboratory, where tremetone assays for our study were performed, has identified tremetone in 9 of 22 tissue samples, including liver tissue but not urine samples, from animals strongly suspected of having *E rugosum* toxicosis.<sup>34</sup> Despite use of this advanced assay and rapid collection of samples, including liver samples from 2 horses that apparently ingested white snakeroot, tremetone was not detected. Thus, it is possible that development of pasture myopathy in horses in our study may not have been associated with ingestion of tremetone-containing plants. Alternatively, false-negative results may have been obtained with the tremetone assay because toxicokinetic studies of tremetone have not been performed to determine the expected concentration of toxin in the urine or tissue at the time of toxicosis.<sup>1</sup> Thus,

at present, this assay cannot be used to definitively rule out white snakeroot toxicosis.

In the study reported here, cool nights and warm days without snow cover may have contributed to pasture myopathy by limiting the growth of natural grasses and encouraging horses to forage on other potentially toxic plants. In addition, these conditions may have modified plant metabolism and altered or enhanced the toxicity of plants such as white snakeroot.<sup>35</sup> However, weather conditions; seasonality; and clinical signs, clinicopathologic findings, mortality rate, and postmortem findings of horses closely resembled those associated with AM.<sup>11</sup> Suspected cases of AM have been reported in many European countries, Australia, and Canada, and white snakeroot does not reportedly grow in areas in which horses are affected by AM.<sup>11</sup> In the United States in 1966, 5 horses were suspected of having AM.<sup>36</sup> Similar to that detected in horses with AM,<sup>12,37</sup> clinical findings in horses in our study were seasonal and associated with wet weather, with rainfall and thunderstorms occurring 1 to 3 days prior to admission for 12 and 4 horses, respectively. Similar to horses with AM,<sup>11,12,14</sup> all horses in our study had been maintained on pasture for at least 14 hours each day during a time of year when pasture growth is minimal. Other similarities to horses with AM detected in our study included the acute onset (median, 16 hours) of clinical signs as well as the specific groups of muscles affected.<sup>11,13</sup> Atypical myopathy affects postural and respiratory muscles, which are typically active in resting horses and have a high oxidative capacity.<sup>11</sup> In addition, in our study, pathologic lesions in skeletal muscle were more extensive than myocardial lesions, similar to lesions detected in horses with AM. In 2 reports<sup>12,38</sup> of AM, histopathologic changes in cardiac muscles were not detected, which is consistent with postmortem findings in 2 horses in our study and 2 surviving horses in which serum troponin-1 concentrations and heart rates at discharge were within reference ranges. Histopathologic lesions such as hyper-eosinophilic fibers, loss of cross-striations, and pyknotic nuclei with or without multifocal hemorrhages in the myocardium reportedly associated with AM<sup>11</sup> are similar to findings in our study. Cardiac arrhythmias and murmurs are reported in some horses with AM<sup>11</sup> but were not identified in horses in our study. Another difference between horses with AM and horses in the study reported here was the relatively small number of horses affected on farms in Minnesota. In the study reported here, the majority (10/14) of affected horses were isolated cases, whereas as many as 115 horses in a pasture may be affected in an outbreak of AM.<sup>39</sup> The cause of AM is suspected to be an ingested or enterically produced toxin (eg, bacterial toxin, mycotoxin, or phytotoxin).<sup>11</sup>

An antioxidant deficiency may play a role in the pathogenesis of AM.<sup>11</sup> In the study reported here, marked lipid accumulation in oxidative muscle fibers and muscle fibers undergoing necrosis were unexpected histochemical findings. It is possible that a nutritional deficiency or toxicity causes seasonal pasture myopathy attributable to disruption of lipid metabolism or oxidative phosphorylation. The accumulation of lipids in the muscular fibers of skeletal muscles and myocardium has been reported in cases of AM.<sup>39</sup> In our study, of the 2 horses that survived, 1 horse was more severely affected (serum CK and AST activities in this

horse were 256,103 and 7,841 U/L, respectively) than the other. Mild lipid storage was detected in muscle biopsy specimens obtained from that horse; however, it responded to aggressive treatment with antioxidants, anti-inflammatories, and fluids. Early recognition and treatment may be key factors associated with a successful outcome for horses with seasonal pasture myopathy.

A seasonal myopathy, characterized by primary acute severe skeletal muscle necrosis and, in many cases, myocardial degeneration, exists in Minnesota. Although there is evidence that a few of the horses in the study reported here had been exposed to white snakeroot plants, the suspected toxic component, tremetone, was not detected in hepatic tissue or urine from any of the 7 horses tested for tremetone. Further studies are necessary to determine the concentration of tremetone in tissues or urine of tremetone-intoxicated animals and the physiologic mechanisms of white snakeroot toxicity. Numerous similarities exist among cases of seasonal pasture myopathy and AM in Europe. Further research is needed to determine the underlying cause of AM and to determine whether cases of seasonal pasture myopathy in the United States share a similar etiology.

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