Denervation atrophy in three horses with fibrotic myopathy

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- Equine fibrotic myopathy has been thought to result from healing of an injury to muscles of the thigh. However, it is likely that the functional abnormality associated with fibrotic myopathy can result from a variety of underlying lesions.
- Peripheral neuropathy should be considered a possible cause of, or a factor in, fibrotic myopathy.

A 14-year-old Quarter Horse gelding (horse 1) was referred for evaluation of a stiff gait in both hind limbs that had developed 6 months previously, approximately 1 month after vaccines were given IM in the caudal thigh. Information concerning the vaccines given and the exact site(s) of injection was not available; however, the owner reported that the horse was getting progressively worse and had lost weight. Treatment with vitamin E, selenium, methocarbamol, and nonsteroidal anti-inflammatory drugs was ineffective.

On physical examination, atrophy of and loss of tone in the gluteal and biceps femoris muscles were noticed. The hind limbs were straight, and there was a bilateral hind limb gait abnormality. The stride was shortened, and the tarsus extended abruptly at the end of the swing phase, resulting in a sudden "slapping" of the hoof onto the ground. The gait abnormality was more severe in the right than in the left hind limb. The horse was not ataxic or parietic.

Palpation and ultrasound examination suggested that there were fibrous bands bilaterally in the biceps femoris muscles. Results of a CBC, serum biochemical analyses, and D-xylose absorption test were all within reference limits, as were blood selenium concentration and serum glutathione peroxidase activity. A sample of CSF contained a slightly high protein concentration (102 mg/dl; reference range, 0 to 70 mg/dl).

General anesthesia was induced. Concentric needle electromyography failed to detect spontaneous activity in any of the muscles of the hind limbs or in the paraspinal musculature. Biopsy specimens were obtained from the biceps femoris, lateral vastus, and semitendinosus muscles, and processed for frozen-section histochemical analysis. At surgery, these muscles all appeared paler than normal. A sample of a sensory nerve, the caudal cutaneous femoral nerve, was fixed in formalin and processed for routine histologic examination.

Histochemical examination of the biceps femoris and semitendinosus muscle specimens revealed a mild increase in fiber size variation, compared with normal; rare angular atrophied fibers; mild to moderate increase in numbers of internal nuclei, compared with normal; and an apparent decrease, compared with normal, in number of type 1 fibers. Abnormalities were not detected in the peripheral sensory nerve or in the lateral vastus muscle specimens.

A clinical diagnosis of bilateral fibrotic myopathy was made. The horse's condition appeared stable during a 3-week period of hospitalization; a bout of muscle trembling, lasting several minutes, was mentioned in the medical record, but details were not recorded. The owner requested that the horse be euthanized, and a necropsy was performed. Neither fibrous bands nor fibrous foci were found within the thigh musculature, even though they had been suspected clinically. The right semitendinosus muscle was diffusely pale, as was the distal quarter of the right biceps femoris muscle. Other gross abnormalities were not seen. Samples of brain; cervical, thoracic, and lumbar portions of the spinal cord; ventral spinal nerve roots; and right and left sciatic nerves in the middle portion of the thigh were obtained for routine histologic examination. Samples of the right semitendinosus muscle, proximal portion of the right biceps femoris muscle, and right intermediate vastus muscle were processed for frozen-section histochemical analysis. In addition, samples of skeletal muscle from both hind limbs, including the pale portion of the right biceps femoris muscle, were clamped, fixed in formalin, and processed for routine histologic examination.

Lesions were not found in sections of brain,
spinal cord, or ventral spinal roots. Sections of right and left sciatic nerves contained mild active degeneration of axons and myelin sheaths, with mild loss of myelinated fibers. Histologic examination of a specimen from the distal portion of the right biceps femoris muscle revealed severe large- and small-group atrophy of myofibers. Clinically important lesions were not seen in the other formalin-fixed muscles that were examined. Severe small-group angular atrophy of type 1 and type 2 fibers was seen in frozen sections of the right intermediate vastus muscle, and individual and small-group angular atrophy of type 1 and type 2 fibers were seen in frozen sections of the right biceps femoris muscle (Fig 1). The histopathologic diagnosis was mild bilateral chronic neuropathy with moderate to severe denervation atrophy of skeletal muscle.

A 35-year-old Quarter Horse mare (horse 2) was examined because of a stiff gait in the right hind limb that had developed 2 years after a similar gait was first noticed in the left hind limb. Severe hind limb ataxia also had developed within the previous week. The mare was thin, and there was prominent atrophy of the caudal thigh muscles bilaterally. Neurologic examination revealed severe hind limb ataxia and a bilateral hind limb gait abnormality characterized by an abrupt cessation of the swing phase. Marked fibrous thickening of the distal portion of the semitendinosus muscle was palpable bilaterally. Cerebrospinal fluid analysis did not reveal any abnormalities. Results of serum biochemical analyses were unremarkable, other than slightly high creatine kinase (717 IU/L; reference range, 143 to 531 IU/L) and aspartate aminotransferase (548 IU/L; reference range, 193 to 509 IU/L) activities. The clinical diagnosis was bilateral fibrotic myopathy and spinal cord white matter degeneration localized to an area between the third thoracic and the third lumbar segments.

The horse was euthanatized, and a necropsy was performed. Pertinent gross necropsy findings were a large (approx 15 × 10 cm) area of severe fibrosis involving the distal portions of the left semitendinosus and semimembranosus muscles, and a severe thickening and fibrosis of the insertions of these muscles. The portion of each muscle proximal to the area of fibrosis was pale and soft. A similar but slightly less-extensive area of fibrosis and muscle atrophy was seen to involve the distal portions of the right semitendinosus and semimembranosus muscles. Necropsy specimens, including the lumbar portion of the spinal cord, spinal nerve roots, left and right sciatic nerves from the middle portion of the thigh, left and right axillary nerves, and insertion of the right semitendinosus muscle, were fixed in formalin and processed for routine histologic examination. Specimens taken from the middle portion of the belly and from the superficial and deep portions of the distal part of the right semitendinosus muscle were processed for frozen-section histochemical analysis. Specimens from the right semimembranosus, deep digital flexor, intermediate vastus, and medial vastus muscles also were prepared for histochemical analysis.

Examination of all spinal cord sections revealed moderate degeneration of myelinated fibers within the dorsal, ventral, and lateral funiculi. Mild axonal degeneration was detected in the left axillary nerve, but lesions were not detected in the right axillary nerve. Mild to moderate degeneration of axons and myelin sheaths and loss of myelinated fibers were seen in the ventral and dorsal nerve roots, and in the left and right sciatic nerves. Sections of formalin-fixed right semitendinosus muscle contained disorganized bundles of dense fibrovascular connective tissue merging with entrapped skeletal muscle fibers and rare adipose cells. The entrapped myofibers varied considerably in size, with numerous small, rounded or angular, atrophied fibers, and fewer numbers of severely hypertrophied fibers and fibers of normal diameter (Fig 2). Numerous fibers had ≥ 1 internal nuclei. Intra muscular nerves had severe loss of myelinated fibers (Fig 3). Examination of frozen sections of the right semitendinosus muscle revealed increased fi-
Figure 3—Photomicrograph of an intramuscular nerve in the perimysium of a section of the semitendinosus muscle shown in Figure 2. There is severe loss of myelinated fibers; only 1 myelinated fiber is visible (arrow). Masson trichrome stain; bar = 25 μm.

ber size variation, compared with normal, at all levels and scattered angular, and atrophied, as well as hypertrophied, type 1 and type 2 fibers. Lesions were most severe in the distal and deep distal portions of the muscle. Focal fiber-type grouping of type 1 fibers was seen in the section from the middle portion of the belly of the muscle. Cytoplasmic disorganization, as evidenced by irregular NADH staining and increased numbers of internal nuclei, was seen in the distal portions of the semitendinosus muscle. Angular atrophy and cytoplasmic disorganization also were seen in the deep digital flexor muscle. There was severe fibrosis and thickening of the perimysium of the distal portion of the semitendinosus muscle, but only mild, focal endomysial fibrosis. Rare scattered necrotic fibers were seen in the distal portion of the semitendinosus muscle. There was a mild increase, compared with normal, in fiber size variation in the semimembranosus muscle, and a high percentage of fibers (approx 50%) had internal nuclei. Only mild angular atrophy of myofibers was seen in the medial vastus muscle. In the intermediate vastus muscle, one of several intramuscular nerves was hypercellular, had a thicker-than-normal endoneurium, and had fewer large diameter myelinated fibers than expected. The frozen section of the distal portion of the semitendinosus muscle contained an intramuscular nerve with prominent endoneurium and fewer large diameter myelinated fibers than expected. The histopathologic diagnosis was mild to moderate chronic axonal degeneration of the spinal cord white matter, nerve roots, and peripheral nerves; mild to severe chronic denervation atrophy and focal reinnervation of skeletal muscle; and severe localized perimysial fibrosis.

A 17-year-old Standardbred mare (horse 3) with left hind limb fibrotic myopathy was donated. The mare had raced successfully until it suffered a pelvic fracture. The mare was severely lame immediately after the fracture occurred, but the lameness resolved, and the mare had been a brood mare for the past 10 years. Further details of the fracture and subsequent lameness were unavailable. In the 2 to 3 years prior to donation, the mare had gradually developed a stiff, staggering gait, characteristic of fibrotic myopathy, in the left hind limb.

On physical examination, the left semitendinosus, semimembranosus, and gracilis muscles were moderately atrophied. The distal portion of the tendon of the semitendinosus muscle was firm and thickened. The horse was not atactic. Concentric needle electromyography, performed after induction of general anesthesia, revealed dense, sustained spontaneous activity, primarily positive sharp waves and complex repetitive activity, in the semimembranosus muscle, the distal portion of the semitendinosus muscle, and the gracilis muscle. Spontaneous activity was not detected in the proximal portion of the left semitendinosus muscle, or in the corresponding muscles in the right hind limb. The diagnosis was denervation atrophy of the left gracilis, semimembranosus, and distal portion of the semitendinosus muscles.

The mare was euthanized, and a necropsy was performed. Because left sciatic nerve damage was suspected, the pelvic limbs were examined prior to disarticulation at the coxofemoral joint. The edge of the caudal aspect of the left greater trochanter was rough, and 2 bone and cartilage fragments were found embedded in dense connective tissue in the canal formed by the head of the femur and the tuber ischidum. The sciatic nerve at this site was embedded in dense connective tissue and was thickened (approx twice normal diameter) and firm. The distal half of the left semitendinosus muscle was severely thickened and fibrotic (approx 6 cm wide × 5 cm thick), and the portion of muscle just proximal to this area consisted of fibrous tissue admixed with pale yellow to red muscle. Muscle tissue deep to the fibrotic area was severely pale, soft, and yellow. The proximal half of the left semitendinosus muscle was grossly normal. The entire left semimembranosus muscle was pale, soft, and yellow, as was the distal third of the left biceps femoris and the cranial third of the left gracilis muscle. Gross abnormalities were not seen in the right hind limb.

Histochmical examination of frozen sections of left semitendinosus, semimembranosus, biceps femoris, and gracilis muscles revealed severe atrophy and hypertrophy of type 1 and type 2 fibers with large- and small-group atrophy, focal fiber-type grouping, type-specific group atrophy, endomysial and perimysial fibrosis, and fat infiltration. Rare, scattered necrotic fibers were seen. Intramuscular nerves seen in 2 muscle sections had severe or complete loss of myelinated fibers with marked endomysial fibrosis. Lesions were not seen in muscle samples from the right hind limb. Examination of formalin-fixed sections of the fibrotic portion of the semitendinosus muscle revealed severe fiber atrophy and hypertrophy, with severe endomysial
and perimysial fibrosis and fat infiltration. A large intramuscular nerve was devoid of myelinated fibers. Sections of left sciatic nerve obtained at the level of the coxofemoral joint were found to be infiltrated and expanded by dense collagenous connective tissue, involving endoneurium, perineurium, and epineurium, with mild to moderate loss of myelinated fibers (Fig 4). Moderate to severe chronic and active axonal degeneration was seen in sections of the left tibial nerve. Similar but less severe lesions were seen in sections from the left peroneal nerve. Only very mild loss of myelinated fibers was detected in sections of the right tibial and peroneal nerves. Lesions were not seen in the lumbar or sacral portions of the spinal cord or in the spinal nerve root sections. The pathologic diagnosis was severe, chronic left sciatic nerve degenerative neuropathy secondary to traumatic fracture of the caudal aspect of the left greater trochanter, with associated chronic and active denervation atrophy and reinnervation of skeletal muscle.

In all 3 of these horses, a presumptive diagnosis of equine fibrotic myopathy was made. Equine fibrotic myopathy is thought to result from healing of an injury to the muscles of the thigh, specifically the semitendinosus, semimembranosus, and biceps femoris muscles. Equine fibrotic myopathy also may involve the gracilis muscle, but the distal portion of the semitendinosus muscle is most commonly involved. All 3 horses had the characteristic abnormal gait (i.e., shortened cranial phase of the stride with sudden caudal movement of the foot prior to placement on the ground) typically associated with equine fibrotic myopathy. This gait is believed to result from restriction of limb movement secondary to adhesions between the affected semitendinosus muscle and the adjacent semimembranosus and biceps femoris muscles. Horses with fibrotic myopathy usually have a history of some trauma, such as IM injections, wire cuts, a fall, or catching a limb in a halter or hobbles, preceding the onset of clinical signs, but in some horses, previous trauma is not reported. Horset 1 developed signs after receiving IM injections, and horses 2 and 3 developed signs after suffering a pelvic fracture. Horse 2 did not have a history of trauma. Equine fibrotic myopathy most commonly affects only 1 hind limb, but bilateral involvement, as in horses 1 and 2, has been reported. In horses with fibrotic myopathy, palpation of the affected limb commonly reveals a firm, thickened area on the caudal surface at the level of the stifle joint, but this thickening is not always found. Horses 2 and 3 had fibrous thickening of the tendon of the semitendinosus muscle in the affected limbs, but horse 1 did not have palpable evidence of fibrosis in this area. Horses with fibrotic myopathy do not typically have clinical signs of spinal cord disease (e.g., paresis, ataxia). Horse 2 had profound ataxia as well as fibrotic myopathy; however, the ataxia was determined to be a result of spinal cord white matter degeneration, and this lesion was thought to be unrelated.

The histologic lesions of severe muscle fiber atrophy, infiltration of muscle by adipose tissue, and marked perimysial and epimysial fibrosis, seen in the distal portion of the semitendinosus muscle from horses 2 and 3, are characteristic of equine fibrotic myopathy. Interestingly, similar lesions also are present in chronic denervation atrophy. Horse 1 did not have this characteristic fibrosis and fat infiltration, suggesting that fibrotic myopathy may be associated with a variety of histologic findings in affected muscle. All 3 horses had individual, small-group, and large-group atrophy of type 1 and type 2 muscle fibers, indicating denervation atrophy. The distal portion of the muscles was more severely affected than was the proximal portion. Horse 1 had evidence of mild axonal damage in both sciatic nerves and horse 2 had evidence of mild to moderate damage in both sciatic nerves. Because both horses were > 10 years old, it is possible that the sciatic nerve lesions were a result of age-related degeneration of large myelinated fibers, similar to that found in the equine lateral palmar nerve of older horses. However, a similar proximal to distal increase in severity of axonal damage and denervation atrophy has been found in horses with the Australian form of stringhalt, another disease
associated with a characteristic hind limb gait abnormality. The left sciatic nerve in horse 3 was severely damaged, with marked loss of myelinated fibers in the tibial nerve component. This case demonstrates the value of careful examination of the sciatic nerve at all levels, including the level of the coxofemoral joint, in horses with fibrotic myopathy. Examination of the sciatic nerve in the area of the coxofemoral joint was not performed in horses 1 and 2 because of prior disarticulation of the limb. We believe that, in all 3 horses, peripheral neuropathy was the cause of, or at least contributed to the development of, the fibrotic myopathy.

The neuropathy in horse 3 was apparently a result of fibrosis surrounding the sciatic nerve in the area of the coxofemoral joint following traumatic fracture of the caudal aspect of the greater trochanter. The cause of the neuropathy in horses 1 and 2 was not determined, but the type of trauma that is known to result in fibrotic myopathy could damage nerve as well as muscle. For instance, an injection in the region of the greater trochanter of the femur that resulted in formation of an abscess or injection reaction could damage the sciatic nerve where the muscular branches to the semitendinosus and semimembranosus muscles arise. Studies of pressure palsy in people and experimental animals suggest that small nerves arising from a major nerve trunk are particularly susceptible to pressure-induced damage, because they lack a thick epineural sheath. Only the sciatic nerve trunks, and not the muscular branches, were examined in horses 1 and 2, and this may explain why only mild axonal degeneration was detected. Alternatively, muscle trauma could result in scarring and secondary nerve damage.

It is likely that the functional abnormality in horses with fibrotic myopathy can result from a variety of underlying lesions. Further study will be necessary to determine the incidence of denervating lesions in horses with fibrotic myopathy. However, given that horses often have a residual gait deficit following surgical intervention, we believe that peripheral neuropathy will be found to be common in horses with fibrotic myopathy.

References