Neurodegenerative Diseases of Horses: Equine Motor Neuron Disease and Equine Degenerative Myeloencephalopathy

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Equine Motor Neuron Disease

Equine motor neuron disease (EMND) is an acquired neuromuscular disease of horses first recognized in 1985 and reported in 1990 (Valentine et al., 1994). EMND has been further investigated and the problem appears to be most often identified in horses with no access to grass and/or on diets with poor vitamin E concentrations.

EMND is characterized by degeneration of motor neurons in ventral horn cells and selected brainstem nuclei, which leads to axonal degeneration and denervation atrophy.

Clinical signs include weight loss and muscle atrophy despite an excellent appetite. Animals appear weak and have a very short-strided gait. In addition, they stand with the head and neck very low and often have all four limbs together in a characteristic "hang-dog" appearance. The horses often tremble, have frequent and at times nearly constant shifting of weight, and spend significant amounts of time lying down. Horses affected with EMND often sweat excessively following exercise and show muscle fasciculations. Some horses appear hyperesthetic; these horses are suspected to have lesions in the spinal ganglia.

The lesions resemble amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), although not all of the features of this disease are noted in affected horses. The etiology of EMND is not known, but the fact that there appears to be a predilection for type 1 muscle fibers that are highly oxidative suggests that the damage may selectively attack highly oxidative motor neurons. Some deficiency of antioxidant activity in these horses may explain the clinical and pathological changes observed. In the familial form of ALS in people, the genetic defect involves the gene coding for superoxide dismutase, an enzyme involved in free radical scavenging and thus preventing oxidant type injury to neurons.

Researchers at Cornell University initially recognized and reported EMND that resembles ALS. The disease is characterized by weight loss, tremors, muscle atrophy, sweating, and apparent pain. EMND affects all breeds, although initial reports incriminated Quarter Horses as the most frequently affected. The disease affects both sexes and is primarily a disease of mature horses from 15 months to 15 years of age. In a retrospective study reported by researchers at Cornell in 1993, the mean age was 9 years. A majority of the horses had been housed in boarding stables with very limited or no access to pasture. The breeds which have been reported to be affected with EMND include Appaloosa, Quarter Horses, Thoroughbreds, Standardbreds, Tennessee Walking Horses, Arabians, Morgans, ponies, and mixed-breed horses. The disease is usually sporadic involving only one horse at a stable. In Ohio, we have observed EDM in 12 horses, primarily Quarter Horses and Thoroughbreds and of both sexes. Although the disease has been reported in many states, there appears to be a clustering of cases in the northeastern United States and Canada.

The clinical signs can begin as progressive weakness and lameness, but progress to profound weakness, sweating, and muscle atrophy. The rate of progression may be one month to several months. By way of example, we examined an eight-year-old Quarter Horse mare presented for weight loss, tremors, muscle atrophy, and apparent generalized pain. In this case, the mare began showing

tremors, pain, and excessive sweating approximately two months prior to presentation. Despite the weakness and tremors, her appetite remained very good. A ravenous appetite with weight loss is often reported in horses with this disease. Aside from these findings on physical examination, there was no evidence of infectious or inflammatory disease observed (complete blood count and fibrinogen were within normal limits). In most affected horses, there is a mild elevation of serum creatine kinase and aspartate aminotransferase.

Besides sweating, tremors or fasciculations, muscle atrophy, and weakness, most horses exhibit a cautious short-strided gait and spend a considerable amount of time in recumbency. When standing, affected horses often hold their head and neck very low and have all four legs grouped tightly together under the center of the body. Recent work by Jackson et al. demonstrated evidence of a distinct retinopathy. This lesion is additional evidence for this disease being a deficiency of nutrition-derived antioxidants such as selenium or vitamin E.

The diagnosis of EMND can be made by a history of progressive weakness in a horse that has little or no access to green forage. An increased incidence has been observed in the northeastern portion of the United States. The disease is observed with a higher likelihood in Quarter Horses (odds ratio = 2.3) (de la Rúa-Doménech et al., 1995). Coupled with clinical signs, biopsy of a specific motor nerve, such as the spinal accessory nerve, is useful. Because the disease primarily affects type 1 muscle fibers, it has been demonstrated that biopsies of the dorsal coccygeal muscles may be an excellent site for muscle biopsy with little evidence of disfigurement.

The clinical signs and the degree of pathology can arrest at any level. Whatever amount of spinal cord and muscle pathology exists at the time of diagnosis will be permanent. Some horses appear to stabilize when placed on large doses of vitamin E or when allowed free access to pasture.

Clinical and pathological lesions of EMND may be observed on the retina of affected horses. The loss of the antioxidant protection of vitamin E appears to lead to haphazard pigmentation of the tapetal and nontapetal fundus in horses (Cutler et al., 2000). This pigment is ceroid-lipofuscin and is likely related to oxidative stress of the retina. The diagnosis should be based on the finding of clinical features and typical muscle and nerve biopsy changes. The presence of ocular changes alone needs to be distinguished from senile retinopathy and is only suggestive of EMND disease when identified by itself.

At postmortem examination, careful evaluation of the muscles, peripheral nerves, nerve roots, and spinal cord should be performed. Atrophy and degeneration of peripheral nerves and muscle may result from the primary lesions. Affected horses show moderate to severe diffuse muscle atrophy of cervical, trunk, and limb musculature. Serous atrophy of fat was noted in only 2 of 23 horses examined at postmortem and 21 horses had normal or mild loss of fat. Gross softening and discoloration of muscles were noted in 20 horses at postmortem. The muscle changes were most consistently found in the medial and lateral portions of the intermediate vastus muscles and in the medial head of the triceps brachii.

In the brain, neuronal degeneration was consistently found in the facial nucleus and in the motor nucleus of the trigeminal nerve. Primary lesions are found in the motor neurons; spinal cord ventral horn cells; brainstem nuclei V, VII, and XII; and the nucleus ambiguous. Pathologists and neuroanatomists and clinicians at Cornell University have demonstrated that the progressive weakness and muscle-wasting along with the degenerative changes of the nervous system in EMND are comparable to those described in people with ALS. The pathologic process has no inflammatory component but tends to affect muscles that have a higher percentage of type 1 fibers as these are more susceptible to oxidative damage.

The pathologic changes appear to be a result of lipid peroxidation, which leads to a chain of oxidative events liberating free radicals that damage cell membranes. The lipopigment accumulation within the capillary endothelium of the spinal cord supports the hypothesis of EMND being an oxidative disease as these changes are similar if not identical to changes observed in experimental vitamin E deficiency (Divers et al., 1994). In other words, based on the pathologic changes, epidemiological findings of management similarities among affected horses, low blood and tissue concentrations of antioxidants, all support the notion that this disease is an oxidative stress neurodegenerative disorder (Divers et al., 1997).

On histopathological examination, degenerating axons were often pale as a result of loss of Nissl substance; the resulting characteristic lesions are described as "ghost cells." One of the most consistent features is the finding of lipofuscin within the cytoplasm of neurons. Many affected neurons are swollen and chromatolytic. Spheroids, glial scars, and neurons undergoing degeneration are typically seen.

The most prominent lesions in the spinal cord are degeneration of the ventral horn neurons at all levels. Detection of the affected neurons is most easily seen by cutting longitudinal sections through the ventral horns. Active neuronal degeneration is most easy to detect in horses affected for two to three months or less. After several months, the lesions are most often glial scars. Within the tracts of the ventral roots, frequent axonal degeneration is noted along with a few spheroids. Many lesions are found in nerve roots and spinal ganglia. Similar findings are noted in spinal and cranial nerves, and cranial nerve ganglia.

The lesions in skeletal muscles are somewhat variable, but a majority involve angular atrophy of muscle fibers of both type 1 and type 2 fibers. In most cases, muscle atrophy is most severe in type 1 fibers.

Equine Degenerative Myeloencephalopathy

Equine degenerative myeloencephalopathy (EDM) is a neurodegenerative disease affecting light breed horses, and it has a familial predisposition. The genetic predisposition may be related to a need for higher levels of vitamin E in the diet of pregnant mares as well as in their foals. Feeds with low vitamin E include heat-treated pellets, stored oats, and poorly managed hay (Mayhew et al., 1977).

There are no gross pathological findings in horses with EDM. The histological findings are consistent with neuroaxonal dystrophy affecting spinal cord and brainstem sensory proprioceptive relay nuclei and neuronal fiber degeneration within ascending and descending spinal cord pathways, often with the most prominent lesions in the thoracolumbar region. In Quarter Horses, dystrophic neurons and axonal spheroids were observed in the lateral cuneate, medial cuneate, and gracilis nuclei of the caudal myeloencephalon as well as in Clarke's nuclei in the spinal cord (Aleman et al., 2010). When described in disorders affecting humans, neuroaxonal dystrophy is often a nonspecific term referring both to the pathologic finding of swelling of distal portions of axons in the brain and to disorders that feature this finding. Neuroaxonal dystrophy is seen in various genetic diseases, vitamin deficiencies, and ageing.

Infantile neuroaxonal dystrophy is an autosomal recessive disease characterized by arrested psychomotor development at 6 months to 2 years of age, ataxia, brain stem dysfunction, and quadriparesis. Juvenile and adult forms also occur. Pathologic findings include brain atrophy and widespread accumulation of axonal spheroids throughout the neuroaxis, peripheral nerves, and dental pulp.

EDM has been recognized in horses and other equidae for more than 35 years. The condition has been reported in horses from North America, Great Britain, and other parts of continental Europe. EDM is most often seen in young foals while still nursing the dam, although it is sometimes recognized at a later age, for example at weaning. In one paper, lesions indicative of EDM were reported in horses up to 12 years of age (Dill et al., 1989a,b). Breeds that appear to have a hereditary basis include Appaloosa, Standardbred, Paso Fino, Norwegian Fjord, Arabian, Quarter Horse, Welsh Pony, and Haflinger as well as Burchell's zebras (Kane et al., 2010).

Nutritional Management of Other Neurologic Conditions

Nutrition as part of the management of neurological conditions of horses is not limited to vitamin E for the treatment for EDM and EMND. Other problems requiring special attention to diet include cervical vertebral stenotic myelopathy (wobblers), which results from narrowing of the vertebral canal. This developmental condition often requires special attention to the energy level, as well as the calcium, phosphorus, copper, and other trace nutrient concentrations in the diet of pregnant mares and newborn foals.

Over the past 10 years, scientific studies have revealed the remarkable effects that fish consumption has on neurological function. Fish oils contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both of which are omega-3 fatty acids. DHA is essential to brain health because it constitutes between 30 and 50% of the total fatty acid content of the human brain (Young et al., 2005).

Vitamin C is well-known for its antioxidant properties. Although it has not been as widely studied as vitamin E, several studies have examined their combined potential. N-acetylcysteine (NAC) is a precursor of glutathione, a powerful scavenger of free radicals. Glutathione deficiency has been associated with a number of neurodegenerative diseases, including ALS and Parkinson's disease. Although many of these conditions are not significant problems in horses, the potential benefit from various nutritional agents in management of equine disorders should be considered.

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