How to Diagnose Equine Degenerative Myeloencephalopathy in Sport Horses

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1. Background

Neuroaxonal degeneration in the brainstem and spinal cord of horses, termed equine degenerative myeloencephalopathy (EDM) or neuroaxonal dystrophy (NAD), has been reported sporadically in the equine veterinary literature for over 40 years. Eventually, consensus developed that these two conditions have such striking clinical and pathologic similarities that NAD should be considered a localized form of EDM in which degenerative changes in the spinal cord are subtle and easily overlooked.[1,2] Disease has been described in equids of many different breeds, with familial or genetic causes suspected. The author's impression is that NAD/EDM was a common pathologic diagnosis when the disease was first described and then less commonly recognized, only to resurge in the last decade. Whether this resurgence is because of true changes in disease incidence or because of changes in clinical suspicion or knowledge of the disease is unclear. In the author's practice (New Bolton Center [NBC]), there is an increasing diagnosis of NAD/EDM, and affected horses have different clinical presentations from those in earlier literature. These proceedings will focus on clinical observations from recent years, with a brief review of existing literature. For simplicity, the disease will be referred to as EDM.

2. Prevalence and Signalment

The first report of EDM described young horses of several breeds as well as a zebra.[3] After its recognition, EDM was considered a common neurologic disease of horses, representing 23/96 (24%) of horses with spinal cord disease evaluated at Cornell from 1974 to 1976.[4] A later report indicated that EDM remained the most common cause of spinal cord disease in horses at Cornell University; it was diagnosed clinically in 171/383 (45%) horses and histologically in 140/287 (49%) horses from 1977 to 1987.[5] Early reports of EDM described the onset of clinical signs from birth to 1.2 years of age, with a mean onset at 0.4 years.[4] Likewise, out of 43 horses with EDM reported at Cornell from 1978 to 1987, owners reported that approximately 80% showed clinical signs by 14 months of age. However, a few outliers were identified, with 3 horses reported by owners to develop signs at 5, 7, and 12 years of age.[6] As time went on, familial predisposition to EDM was documented in multiple breeds of equids, including Appaloosa, Arabian, Thoroughbred, Standardbred, Morgan, Paso Fino, captive Grant zebras, and Przewalski horses.[7] Approximately 90 horses clinically evaluated at NBC from 2016 to 2020 had a final post-mortem diagnosis of EDM, with the number increasing each year (2016, 4 horses; 2017, 6 horses; 2018, 12 horses; 2019, 28 horses; 2020, 40 horses). Contrary to previous reports, most of the

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sport horses diagnosed by the author are between 5 and 15 years of age, with young to middle-aged Warmbloods making up the bulk of cases diagnosed at NBC. However, Quarter Horses, Standardbreds, Thoroughbreds, Arabians, and horses of many other breeds have also been diagnosed. It is possible that EDM has a delayed onset in Warmbloods, but it is also possible that the perceived later onset is due to management and training differences, causing subtle abnormalities to be missed early in life that only becomes evident when workload and level of performance increase. Many of the Warmblood sport horses diagnosed with EDM have been imported from Europe, but they are not from a consistent region, of a consistent breed, or in the same family line. Importantly, American-bred horses, both Warmbloods and many other breeds, are also affected by this condition.

3. History

Obtaining a thorough history from people familiar with the horse, including owner, trainer, rider, and manager, is very helpful for diagnosing EDM. Although not observed in every case, behavior changes are a very common clinical feature that should alert the veterinarian to the possibility of EDM. The behavior changes cannot always be detected by people less familiar with the horse's "normal" behavior, and hence, veterinarians should listen carefully to the observations of those who know the horse well.

"Personality" changes are common, including changes in the horse's general level of awareness, reaction to stimuli, and interactions with people, animals, and the environment. Many horses eventually diagnosed with EDM are purchased because they are initially perceived to be calm and quiet. Some horses become increasingly dull and lethargic, to the point of appearing sedated, and they seem to lose interest in social interactions with people and other horses. This overly dull/sedate behavior might be interspersed with periods of uncharacteristic anxiety, spookiness, and aggression toward horses, other animals, or people. Other horses appear to be persistently anxious or on edge, often becoming cranky or aggressive. Owners frequently comment "he's not the same horse he used to be."

Bad behavior under saddle is frequently the first sign detected. Horses often start spooking unpredictably and severely. This spookiness might lead clients to suspect eye problems, but ophthalmic exam is usually normal. Many of these horses were considered unusually calm before the onset of uncharacteristic spooking. Even professional riders can rarely predict (or recognize in hindsight) the stimulus for the spook. Although some horses become very reactive to sound and others reactive to visual stimuli, many spook for no apparent reason, often after they have gone past an area uneventfully several times. For example, a horse might canter over a line of fences three times and then on the fourth spook violently in between fences. In addition to excessive and unpredictable spookiness, other bad behaviors are common, including bucking, bolting, rearing, spinning, refusing fences, and becoming unwilling to stand at the mounting block. Importantly, these bad behaviors are a marked change from the horse's normal behavior and are usually unprovoked and unpredictable. Owners frequently use descriptions such as "it was like a switch flipped" or "it was like he didn't know where he was or what happened – he had a glazed/vacant expression" when they describe the episodes. Sometimes clients detect signs that might indicate ataxia and sometimes they do not. It is more common for behavior changes to be the primary reason for evaluation, but suspected lameness or loss of coordination can be the primary complaint. Horses might start knocking rails, struggle with lateral movements, have difficulty holding leads at a canter or changing leads, or feel weak. Tripping with the thoracic limbs and "falling out behind" (tripping, stumbling, or buckling with the pelvic limbs) are common observations. Additional client observations include topline musculature that seems underdeveloped or atrophied and haircoat changes such as a long or dull haircoat. These changes can be reminiscent of a horse with pituitary pars intermedia dysfunction (PPID) and sometimes prompt endocrine testing despite the relatively young age of the horse. Other clients have observed changes in behavior that might result from sensory abnormalities, including abnormal reactions to grooming or being sprayed with water, a perceived inability to sense temperature changes, and abnormal reactions to pressure when asked to move away from the hand on the ground or the leg under saddle.

4. Clinical Signs

Initial descriptions of EDM reported symmetric tetraparesis and ataxia, generally noticed between birth and 1 year of age.[3] These signs reflected upper motor neuron and general proprioceptive tract lesions, with no evidence of cranial nerve, cerebral, or cerebellar involvement. Hypalgesia, hypotonia, hyporeflexia, or muscle atrophy were not observed. These signs were considered indistinguishable from those caused by other focal, multifocal, or diffuse myelopathies affecting the cervical spinal cord. However, most focal myelopathies cause deficits that are slightly more severe in the pelvic limbs than in the thoracic limbs, whereas horses with EDM were often observed to have deficits in the thoracic limbs that were either similar in severity to those in the pelvic limbs or much less severe than those in the pelvic limbs, with a bigger disparity than would be expected for a focal compressive lesion. Curiously, a subsequent report described similar tetraparesis and ataxia but with significant hyporeflexia over the neck and trunk, particularly in horses with a longer duration of clinical signs.[8] This hyporeflexia was evident during assessment of cervical, cervicofacial, laryngeal adductor (slap), and cutaneous trunci reflexes. In the

author's experience, horses with EDM as the sole problem usually appear to be systemically healthy and often are well conditioned or overconditioned, and some have a phenotype consistent with equine metabolic syndrome. Additionally, some relatively young horses diagnosed with EDM have phenotypic characteristics more commonly associated with PPID, including topline muscle wasting and a long, dull haircoat. Even though most owners and trainers observe convincing behavior changes, the horse might appear normal in terms of mental status and behavior during veterinary examination. However, some horses appear unusually dull or sedate during examination. Other horses appear overly anxious and inappropriately spooky when considering their age, breed, and previous experiences. Cranial nerve assessment is usually normal. Rarely, horses will have an inconsistent menace response or hyperreactive menace response with rapid repeated (clonic) blinking. Spinal reflexes are usually normal, although the cervicofacial reflex might be subjectively decreased. Cervical range of motion is typically normal unless concurrent cervical arthritis is present. Dynamic gait evaluation typically reveals proprioceptive deficits and signs of mild-to-moderate ataxia and paresis consistent with a cervical or diffuse myelopathy. Most horses are graded 1 to 2/5 on the modified Mayhew ataxia scale at the time of first evaluation, although occasionally horses show more severe deficits (2.5 to 3/5). Repeated evaluations over months might show a progression of neurologic disease. Evaluation at the walk most frequently reveals a normal-to-long strided gait, sometimes with a "floaty" or toe-flipping appearance. Horses might show irregular foot placement, occasional limb interference, or forging. These signs might be exacerbated by walking with head elevation. Circling the horse in hand tightly in both directions is usually the most helpful test to detect proprioceptive deficits. Horses often show delayed protraction, such that their body leans to the side, but they are slow to initiate limb movement—their feet never seem to catch up with their center of gravity. Limb interference might be seen from the level of the hocks/carpi down to the hooves. The toe of the outside limb might scuff or drag on the ground as it is widely and spastically swung into position. The inside foot might pivot for an abnormally long time on the ground. When the horse is stopped suddenly or asked to rapidly change direction, excessive truncal sway and loss of balance might be observed. Horses often spontaneously place their limbs in unusual positions relative to their center of gravity and then fail to replace them in a more normal position. Deficits are often more obvious in the pelvic limbs than thoracic limbs. When walked down a hill, particularly with head elevation, the horse might overreach or search for the ground with its front feet while scuffing, sinking, or buckling with its pelvic limbs. When observed at the trot, the horse might appear more bouncy or spastic than expected, with difficulty moving in a straight line and a tendency to drift in either direction.

5. Differential Diagnoses

Horses with EDM might be presented for bad behavior under saddle, poor performance, or poor movement and suspicion of lameness. The list of problems that can cause these types of complaints is extensive. The author strongly believes that most horses are quite willing and eager to please and that development of bad behavior in a horse that previously performed well is almost always related to a medical problem. Marked behavior changes in a horse that has undergone no major environmental or training changes are almost always due to pain or brain disease. Therefore, if the primary complaint is abnormal behavior, the owner should be carefully questioned and the horse should be carefully observed for evidence of neck, back, limb, or abdominal pain. The author finds 24-hour video monitoring with behavioral analysis to be helpful with many cases; horses sometimes show very demonstrative and localizing pain behaviors when barns are quiet and no one is interacting with them. If the horse is presented for a vaguer complaint of poor performance or poor movement, careful and potentially repeated orthopedic and neurologic examinations are necessary to determine whether the poor performance and abnormal gait are due to orthopedic disease alone, neurologic disease alone, or a combination of both. Lameness diagnostics such as local anesthesia can help confirm an orthopedic source and narrow down differential diagnoses. If the gait abnormality is not severe enough to assess the effects of local anesthesia (not "blockable"), a phenylbutazone trial might yield helpful information. If the horse's performance improves on phenylbutazone, orthopedic and potentially other painful problems should be investigated. If signs of proprioceptive deficits and ataxia are clearly present, neurologic causes of poor performance and behavior changes should be considered. Horses with EDM typically have a chronic course of disease and often have not been right for months. Ataxia typically is symmetric and affects all four limbs, although the pelvic limbs might be more obviously affected. In the author's practice, most horses with symmetric proprioceptive ataxia of a duration of multiple weeks have one of three following categories of disease: (1) compressive myelopathy, usually due to cervical vertebral stenotic myelopathy (CVSM); (2) infectious myelitis, usually due to equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*; or (3) degenerative myeloencephalopathy (EDM/NAD). Therefore, diagnostic testing is aimed at differentiating between these three types of diseases.

6. Laboratory Results

Standard hematologic tests, including complete blood cell count, serum amyloid A, fibrinogen, and chemistry panel, generally yield unremarkable results unless comorbidities exist. Cerebrospinal fluid (CSF) collection is strongly recommended for horses with neurologic disease, and results can confirm or refute the presence of infectious neurologic disease, with EPM being the infectious disease of most concern. Horses with EDM usually have a normal CSF nucleated cell count (NCC; <5 cells/μL) and normal cytology (very low number of mononuclear cells, without neutrophils, eosinophils, or other abnormal cells). CSF total protein can be normal (<90 mg/dL) or mildly increased; these mild increases are typically in the 90- to 120-mg/dL range. If CSF cytology is abnormal, with increased NCC indicating meningitis, infectious viral and bacterial diseases should be strongly considered. EPM is the most common infectious equine neurologic disease in North America, and specific testing should be considered in most areas of the United States.[9] Horses with EDM might be negative or positive on EPM serologic tests, depending on exposure status. Generally, negative serologic results have a high negative predictive value and rule out EPM. Rare exceptions exist in horses with immunodeficiencies or recent infection, and confirmation with CSF testing should be considered if CSF is available. Positive serologic results have a low positive predictive value but indicate the need for further testing, and more accurate assessment of EPM status should be pursued, ideally by using quantitative antibody testing on paired serum and CSF samples to detect intrathecal antibody production. Although a rare cause of neurologic disease in horses, Lyme disease is a frequent concern of clients and theoretically could cause both behavior changes and ataxia.[10] Horses with EDM might be negative or positive on Lyme serology, depending on exposure status. Diagnosis of neuroborreliosis is very challenging in horses, and antibody levels are not necessarily predictive.[11] Because most true neuroborreliosis cases have abnormal CSF cytology, with neutrophilic or lymphocytic pleocytosis, the author generally discounts Lyme disease as the primary cause of neurologic deficits if CSF cytology is normal, regardless of serum and CSF antibody levels against *Borrelia burgdorferi*. Vitamin E deficiency has been associated with EDM, and vitamin E concentration should be assessed in suspect cases.[7] Low vitamin E concentration (less than 2 ppm or 200 μg/dL) is supportive of EDM diagnosis, particularly when other causes of neurologic disease have been excluded. However, adequate vitamin E status does not preclude the diagnosis of EDM. Many horses diagnosed by the author have vitamin E concentrations well within the normal range at the time of diagnosis. It is possible that these horses were deficient *in utero* or during early stages of their lives, contributing to disease development. The utility of biomarkers such as phosphorylated neurofilament heavy (pNF-H) for diagnosis of equine neurologic disease, including EDM, is under investigation.[12] Current evidence suggests that abnormally high concentrations of pNF-H in serum and CSF are suggestive of EDM if diseases such as EPM have been excluded. However, pNF-H testing has a low sensitivity for EDM diagnosis, and many confirmed cases have normal pNF-H concentrations in blood, spinal fluid, or both.

7. Imaging Results

Survey cervical radiography, cervical myelography, and sometimes cervical myelography-computed tomography are used to assess for CVSM. One of the major challenges in EDM diagnosis is that affected horses might also have cervical arthritis, CVSM, or both. Normal survey cervical radiographs and/or negative cervical myelography make CVSM highly unlikely and increase clinical suspicion for EDM, assuming infectious causes of disease are also excluded. Unfortunately, abnormal cervical radiographs and even positive cervical myelography do not exclude the possibility of EDM because false-positive myelograms are possible and horses can be affected by both diseases simultaneously. With increasing recognition of EDM, the author has become more cautious in recommending surgical cervical fusion for horses with equivocal ("gray zone") myelograms and horses with positive myelograms but behavior changes suggestive of EDM.

8. Postmortem Results

EDM diagnosis currently requires post-mortem examination, but the characteristic degenerative changes can be missed if the pathologist is inexperienced or the brainstem is not carefully evaluated. A diffuse degenerative myeloencephalopathy was initially described by Mayhew et al.,[3] with the most pronounced degeneration in thoracic segments of the spinal cord. Ventral and dorsolateral funiculi, particularly the dorsal spinocerebellar tract, were considered most severely affected, and dorsal funiculi were considered least severely affected. Axonal swelling (dystrophy) and abnormal neuronal cell bodies were seen in the gray matter of the spinal cord and in some brainstem nuclei; the most prominent changes were observed in the spinal cord proprioceptive nucleus (nucleus of the dorsal spinocerebellar tract) and the caudal medullary proprioceptive nuclei (gracile and cuneate, particularly the lateral cuneate nuclei). Mayhew et al.[4] included the summary description "neuronal fiber degeneration throughout the spinal cord (particularly in the dorsolateral and ventromedial tracts), and NAD, lipofuscin-like pigment accumulation, astrogliosis and necrobiosis of neuronal cell bodies in specific brain stem and spinal cord nuclear areas." Around the same time as the above description, Beech [13] described NAD in Morgan

horses, which had similar degenerative changes (NAD, gliosis, vacuoles, and pigment) as horses with EDM; however, these changes were localized to the accessory (lateral) cuneate nuclei, without substantial microscopic spinal cord changes. In the author's experience with sport horses, the brainstem changes are most consistent, particularly in the lateral cuneate nuclei, whereas spinal cord lesions are minimal or difficult to detect.

9. Summary

EDM remains a common cause of neurologic disease in the horse but is almost certainly underdiagnosed due to the challenges in antemortem diagnosis. Practitioners should maintain a high degree of suspicion for this disease in horses with behavior changes and mild-to-moderate ataxia or in any horse with relatively symmetric ataxia that lacks evidence for infectious disease or spinal cord compression. Diagnosis in the living horse is based primarily on exclusion of other potential differential diagnoses through CSF analysis and appropriate imaging. Post-mortem diagnosis requires an experienced pathologist and careful attention to the brainstem, where degenerative changes are most evident.

Acknowledgments

Declaration of Ethics

The Author has adhered to the Principles of Veterinary Medical Ethics of the AVMA.

Conflict of Interest

The Author has no conflicts of interest.

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