How to Diagnose and Treat Neuromuscular Diseases: “The Weak, Trembling Horse”

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1. Introduction

Disease states affecting the lower motor neuron (LMN), neuromuscular junction, or muscles can result in vague clinical signs of weakness and trembling that make these diseases difficult to distinguish from one another as well as from non-neuromuscular problems such as electrolyte disturbances, colic, or pain. Early recognition of neuromuscular disease is important in rapid diagnosis and early, appropriate treatment. Clinical signs in acute cases often include trembling, tachycardia, unwillingness to stand still, an abnormal stance (elephant on a ball), repeated attempts to lie down, and prolonged periods of recumbency. There are several disease processes that have been recognized in the horse that result in these signs either acutely or chronically. This summary describes these diseases and presents a stepwise process that practitioners can use to differentiate the diseases from each other as well as from more common causes of weakness and trembling. In addition, this summary reviews diagnostic and therapeutic options.

2. Botulism

Botulism is one of the more common LMN diseases seen in the horse. The signs seen are the result of a neurotoxin produced by the bacterium *Clostridium botulinum*, an anaerobic, spore-forming rod. Botulism spores are found in soil throughout the United States. There have been eight toxin types identified (A, B, C₁, C₂, D, E, F, and G). More than 85% of cases seen in North America are caused by toxin B. Infection can occur in one of three ways: ingestion of the preformed toxin, ingestion of spores with subsequent elaboration of toxin in the gastrointestinal tract (Shaker Foal Syndrome), or contamination of a wound with spores leading to production and absorption of the toxin. Equine cases usually occur sporadically, whereas bovine cases can be seen as herd outbreaks.

The toxin acts at the presynaptic nerve terminal to block release of acetylcholine into the synaptic cleft. The toxin binds irreversibly to receptors on the presynaptic terminal and is internalized in a vesicle. Because the binding is irreversible, neuromuscular function only improves when nerve endings have been regenerated.

Clinical signs are the result of muscle weakness that may progress to diffuse flaccid paralysis. These signs can occur anywhere from 12 h to 10 days after intoxication or infection. The most classic clinical signs associated with botulism in horses are poor tongue tone and dysphagia. Early signs include generalized muscle weakness, gait abnormal-
ities (stiff/shuffling), decreased ability to eat, and increased episodes of recumbency. These horses have normal mentation because the central nervous system (CNS) is not affected. Cranial nerves remain intact though there can be a decrease in lid tone and pupillary light reflexes.

Diagnosis of botulism is usually presumptive and based on clinical signs, as well as vaccination history. A “grain test” can be performed. This involves feeding 8 oz of grain in a shallow tub. A normal horse should be able to finish the grain in <2 min. Hematology and serum chemistry may reflect dehydration and horses with prolonged difficulty standing can have muscle enzyme elevations. Cerebrospinal fluid (CSF) is normal. Definitive diagnosis is made by the demonstration of toxin in the gastrointestinal (GI) contents, serum, or wounds. The most sensitive test is a mouse bioassay where serum of a suspected horse is injected into a mouse, which is observed for signs of botulism. Mice that have been pretreated with antiserum are also injected and should be protected if the toxin is present. Unfortunately, horses are sensitive to low levels of toxin that may not produce disease in these mice; therefore, many cases of equine botulism are not definitively diagnosed. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) tests have been developed but are not commercially available.

The most important treatment in the management of a botulism case is the administration of antitoxin. The antitoxin binds and neutralizes the circulating toxin. Timing is important because the outcome is favorable in 70% of cases when the antitoxin is administered while the horse is still standing. The prognosis decreases significantly once the horse becomes recumbent and is highly fatal if the antitoxin is not administered at all except in very mild cases. A polyvalent antitoxin is available from the University of Pennsylvania, New Bolton Center. This form of antitoxin is available in 500-ml units, and one unit is usually sufficient for a 500-kg adult horse. A monovalent antitoxin is available from Veterinary Diagnostics Inc. in Templeton, CA. It is important to anticipate a progression in clinical signs for 12–24 h after administration of the antitoxin because it can only bind freely circulating toxin. The toxin that has already entered nerve terminals will still bind with receptors.

The remainder of treatment in these cases is mainly supportive. The dysphagia commonly seen will necessitate nutritional support, either enterally or parenterally. Ileus is another sequelae that may require withholding enteral feeding. Horses that are dysphagic may aspirate. This tendency, combined with prolonged recumbency, predisposes these cases to aspiration pneumonia, and antimicrobial therapy may be necessary. It is important when treating these cases to avoid the use of pharmaceuticals that potentiate the neuromuscular blockade. Aminoglycosides (gentamicin and amikacin) and polymyxin B should be avoided. Lidocaine will also affect neuromuscular transmission and should not be used in these cases. Although these horses have difficulty standing for prolonged periods, resist the urge to place them in a sling. This may lead to struggling, exhaustion, and increased mortality. Mechanical ventilation may be required in the most severe cases and is feasible in foals but is not usually possible in the adult horse.

Outcome and duration of recovery are dependent on the amount of toxin that is initially present in the circulation. Prognosis is difficult to determine at the onset of clinical signs, and success can be dependent on the secondary complications of recumbency such as pneumonia and decubital ulceration. A highly effective vaccine is available in North America but only protects against type B toxin. Horses in endemic areas should be vaccinated.

3. Equine Motor Neuron Disease

Equine motor neuron disease (EMND) is a more recently reported disease of horses. It is associated with decreased serum vitamin E levels, and the disease can be reproduced by holding horses off fresh grass pasture for months to years and feeding low vitamin E diets. Small intestinal malabsorptive diseases could also lead to low levels of vitamin E and other antioxidants. Because histopathologic changes are similar to those of amyotrophic lateral sclerosis (ALS), oxidative stress likely is involved in the observed neuronal injury and denervation. These changes are especially seen in type I myofibers, which are more oxidatively active than type II fibers.

Clinical signs are reflective of the skeletal muscle denervation and include generalized weakness and muscle atrophy. The onset can be insidious or acute. It is not uncommon for these cases to present for chronic weight loss because of the chronic nature of the muscle atrophy. As the postural (antigravity) muscles are predominately affected, trembling and increased periods of recumbency are often seen. These horses also stand in a characteristic position of an “elephant on a ball” with all four feet placed close together to better distribute weight over all four weak limbs. These animals also frequently shift their weight and are more comfortable walking than standing. Thus, they are often perceived to be anxious or in pain. Head carriage in these cases is often low, and there can be wasting of the neck and shoulder musculature. Conversely the tail head in these cases appears elevated because of the atrophy of the coccygeal muscles. Mentation and cranial nerves are unaffected, and no proprioceptive ataxia is seen in these cases. In some instances, fundic examination will show deposition of brown-black or yellow-brown lipofuscin pigment at the tapetal–non-tapetal junction.
Diagnosis is based on clinical signs and history of poor access to green forage. The most consistent biochemical abnormality in these cases is hypovitaminosis E. Increases in muscle enzyme activity may be present in acute cases but may also be normal in more chronic states. There are no typical changes seen in CSF. Muscle or nerve biopsies will show denervation. These changes along with appropriate clinical signs are needed for a definitive diagnosis of EMND. The muscle biopsy is the most common invasive diagnostic. The sacrocaudalis dorsalis medialis, the tailhead muscle, is predominantly type I fibers and highly sensitive to denervation. This sample can be easily obtained with sedation and local anesthesia.

Vitamin E supplementation is the recommended treatment for EMND. This can be given as a fresh source of grass or alfalfa or oral vitamin E supplements. Natural vitamin E supplements have been shown to have a higher bioavailability than the synthetic versions. Unfortunately, there has been no clinical trial showing that vitamin E supplementation is effective in halting or improving the disease process. Although some cases show improvement or stabilization of clinical signs initially, long-term prognosis is poor, and many cases are ultimately euthanized.8

4. Electrolyte Abnormalities
Mild to moderate electrolyte aberrations can lead to diffuse weakness similar to LMN disease, but these signs are reversed with correction of the abnormalities. Hypokalemia can lead to lethargy and weakness and myopathies. This can often be seen with concurrent hypomagnesemia. Low serum levels of magnesium can lead to muscle fasciculations, restlessness, and weakness. Hypocalcemia is another electrolyte abnormality that can lead to muscle weakness and recumbency. Most of these derangements are seen secondary to an inciting disease process and can be easily identified on a serum biochemistry profile. Correction of these abnormalities should be complete before evaluating the horse for neuromuscular disease.9

5. Hyperkalemic Periodic Paralysis
Hyperkalemic periodic paralysis (HYPP) is caused by a mutation passed on by the Quarter Horse stallion “Impressive” and subsequent descendants. It is not a disease of lower motor neurons nor is it characterized by true weakness. This disease does share clinical signs with LMN disease and may be confused with LMN diseases. HYPP episodes can lead to diffuse muscle fasciculations and recumbency. These signs are usually secondary to an exercise event and are temporary, and these cases also have known predisposition (if pedigree or genotype is documented). If a Quarter Horse is seen with muscle fasciculations or in recumbency, appropriate treatment for hyperkalemia (dextrose, calcium, ± bicarbonate) should be initiated if the horse is known to be HYPP homo- or heterozygous or if HYPP status is unknown.

6. Other Myopathies
Two additional myopathies, polysaccharide storage myopathy (PSSM) and recurrent exertional rhabdomyolysis (RER), warrant mention because these cases can present with similar clinical signs. Like HYPP, these myopathies are often associated with recent exercise. RER is more often described in Thoroughbreds, whereas PSSM is associated with Quarter Horses and Draft breeds. The exact mechanism that causes RER has not been identified, but it is thought to be a defect in calcium regulation. PSSM is a result of accumulation of abnormal polysaccharide. Significant accumulation occurs over time, and signs may not been seen in the first few years of life.10

Clinical signs for both diseases include signs of cramping, stiff gait, muscle fasciculations, anxiety (sweating, tachycardia), refusal to move, and sometimes recumbency. Signs are mainly limited to the muscles of the hindquarters (gluteal and quadriceps), but the front limbs may also be affected. Muscles are firm and painful on palpation.

Biochemical abnormalities are also similar for both RER and PSSM. The hallmarks of these diseases are severe elevations in serum creatine kinase (CK) and aspartate aminotransferase (AST) enzyme activities caused by their release from damaged muscle fibers. CK rises rapidly and peaks within 4–6 h of exercise and can exceed 100,000 U/l. Typically, AST levels take 12–24 h to reach maximum levels. If there is no longer any ongoing muscle damage, the CK levels should rapidly decrease over 24–48 h, whereas AST levels will take 4–7 days to return to normal.11 This severe muscle damage also leads to the release of myoglobin and subsequent myoglobinemia. The high level of myoglobin is filtered by the kidney, which will cause myoglobinuria and pigment nephropathy. It is therefore important to perform a urinalysis in these cases. The urine will be dark colored and will not clear with centrifugation. Myoglobinuria can easily be distinguished from hemoglobinuria by showing that the serum is clear when spun down.

Clinical signs, history of recurrent episodes of myopathy, and biochemical abnormalities only provide a presumptive diagnosis. Pre- and post-exercise CK and AST levels may help confirm suspicions and aid in the diagnosis of subclinical exercise-induced myopathies. To definitively diagnose these diseases a muscle biopsy (± genetic testing) is required. The most commonly sampled muscle is the semimembranosus muscle. The sample can be evaluated for the presence of abnormal polysaccharides or evidence of recurrent myopathy.

Immediate treatment of these episodes should involve correcting dehydration and providing analgesia. Care should be taken in administering nephrotoxic drugs such as non-steroidal anti-inflam-
matories (NSAIDs) to a dehydrated horse with a potential nephropathy. Horses should be stall-rested until their muscle enzyme activity levels return to normal before returning to exercise. Kidney function should be monitored closely during this time, especially when NSAIDs are being administered.

Specific treatments can include dietary and exercise changes. Thoroughbreds with RER may benefit from a lower stress environment and training schedule and a diet that does not provide excessive calories for the work being done. Horses diagnosed with PSSM do well when they are maintained at a good level of fitness. Exercise intensity should be increased slowly, and affected animals may benefit from living in a field where they can move freely. Both RER and PSSM cases should be fed a high-fat, low-carbohydrate diet.

There are other, less common myopathies that can occur. The diagnosis and initial treatment plan is largely the same as with RER and PSSM.

7. Colic

The signs of acute LMN disease can easily be confused with acute abdominal pain. Restlessness, muscle fasciculations, and recumbency can be a sign of colic as well as muscle weakness. A thorough colic examination should be performed. This includes a rectal exam (if safety allows) and nasogastric intubation. In these cases, sedation with α-2 agonists and analgesia may be diagnostic and palliative. Cases of neuromuscular disease will not readily improve with sedation and analgesia. Also, keep in mind that colic and neuromuscular disease can be concurrent, because many botulism cases have ileus and the potential for a surgical gastrointestinal lesion. Care must be taken in the diagnosis of these cases.

8. Methods for Diagnosis

When presented with a case that shows signs compatible with diffuse muscular weakness, it is important to obtain a thorough history (Fig. 1). Always obtain a complete vaccination history and feeding regimen, including access to pasture. Pertinent questions should show the duration of the condition. If it is an acute episode, inquire about the animal’s activities before the onset such as exercise and any abrupt changes in feed or activity level. In the case of Quarter Horses, a full pedigree and/or HYPP genotype results, if available, should be obtained. A full physical examination should begin with observation of the animal at a distance. As mentioned previously, a colic examination should be done to rule out abdominal discomfort as a cause of the perceived muscle weakness. In addition, a full neurologic examination should be done to rule out CNS disease, and a fundic examination should also be performed.

Simple hematology and serum biochemistry can be helpful in ruling out electrolyte abnormalities or primary myopathies. A packed cell volume (PCV) and total protein will indicate dehydration and serum muscle enzyme activities can indicate the duration of the episode and may implicate a myopathy as opposed to a neuromuscular disease. Serum vitamin E levels should be measured. A urinalysis should be performed to discover pigmenturia, assess renal function, and look for casts as a sign of nephropathy.

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**Fig. 1.** Step-wise plan for the diagnosis of neuromuscular disease.
Once abdominal discomfort and electrolyte abnormalities have been ruled out, more extensive or invasive diagnostics can be considered. Muscle biopsies can be helpful in the diagnosis of neuromuscular diseases and myopathies. If there is question as to whether a myopathy or neuromuscular disease is the cause of the clinical signs, biopsies of both the semimembranosus muscles and the sacrocaudalis dorsalis medialis muscles should be submitted.

In chronic cases that involve weight loss, a more extensive work up should be done to rule out gastrointestinal disorders that could lead to poor absorption of nutrients including vitamin E. Glucose absorption testing or abdominal ultrasound may provide further information regarding the absorptive ability of the small intestine.

9. Treatment

Treatment should be appropriate for the diagnosed disease process as previously mentioned. If botulism is suspected and financial resources allow, botulism antitoxin should be administered as soon as possible. Vitamin E supplementation can be implemented even while testing is still being processed. Supportive care should include correction of dehydration and any electrolyte or acid–base abnormalities. Nutritional support can be provided through a nasogastric tube or parenterally if needed. Animals that are persistently recumbent must be managed for pressure sores and potential pneumonia.

10. Conclusion

Neuromuscular diseases caused by LMN dysfunction are an uncommon event but should be kept in mind when evaluating a case with diffuse muscle weakness. By following Fig. 1, simple steps can be taken to properly differentiate and diagnose neuromuscular disease.

References