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Investigation and Management of Horses with Exertional Rhabdomyolysis

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There are many historical, somewhat speculative reports suggesting different possible causes of equine exertional rhabdomyolysis (ER).[1] A large number of causes is unsurprising given the numerous acquired and inherited forms in humans, [2] however, since certain types of equine ER appear to have underlying genetic causes, the intermittent and varying severity of phenotype in these animals may be explained by the influence of modifying genes and environmental factors: factors that in the past were determined to be the primary etiology. Episodes of rhabdomyolysis not generally associated with exercise may be of toxic, infectious, immune-mediated or iatrogenic origin. The recent identification of certain specific forms of ER means that classification can now be based on the underlying aetiopathogenesis.

HISTORY AND PRESENTING COMPLAINT

Often the history includes training or management changes. The complaint may vary from a mild stilted gait to severe stiffness, sweating or recumbency[3] however most animals are mildly - moderately af fected. During an attack, horses with ER show varying clinical signs. Mildly - moderately af fected animals are tachycardic, with firm painful hindlimb, epaxial and gluteal musculature causing gait stiffness.[3] Pigmenturia may be evident, especially in more severe cases. These animals are often extremely painful, tachycardic, hyperthermic and tachypneic; they sweat profusely and may be totally unwilling or unable to move.[3] These horses have widespread muscle involvement and may become recumbent. The worst affected animals may show signs compatible with underlying shock and disseminated intravascular coagulation.

LABORATORY EXAMINATION

Routine clinicopathologic changes in mild cases usually consist solely of elevations in the activities of the muscle-derived enzymes, CK and AST. CK is the most convenient and specific marker of acute muscle damage and peaks at 4 to 6 hours following muscle damage and (unless the damage continues) starts to decline, with a half-life of approximately 12 hours.[4] AST activity peaks about 24 hours after an episode and may remain elevated for several days to weeks. Although both CK and AST activities rise in proportion to the degree of muscle damage, they do not always reflect the severity as assessed clinically or the prognosis. More severe cases have additional less specific abnormalities. Hyperkalemia may reflect the release of potassium from damaged muscle fibers. The hematocrit and total protein may rise due to intracompartmental fluid shifts. High serum creatinine concentration suggests the possibility of acute renal failure. Complex acid-base abnormalities are sometimes present as the usual hypochloremic metabolic alkalosis[5] shifts to metabolic acidosis if shock ensues. Widespread hematological and biochemical abnormalities are evident in terminal cases.

A urine sample collected early during treatment may, with microscopic examination, reveal urinary casts, a useful indicator of tubular necrosis and impending acute renal failure, prior to the plasma creatinine concentration rising. Reagent strip analysis of urine does not differentiate myoglobin from haemoglobin, therefore specific assays are required to determine the cause of any pigmenturia. However, measurement of urinary myoglobin concentration is not usually necessary in an animal with significantly elevated serum muscle enzyme activities. The calculation of electrolyte clearance ratios (see below) during an episode of ER may help evaluate renal function, but should not be used to determine whether electrolyte imbalances were responsible for precipitating the attack.

Differential diagnosis

In the acute form, the disease may be confused with colic, laminitis, tetanus, hyperkalemic periodic paralysis and some cardiac arrhythmias. However, usually these diseases are readily distinguishable by additional signs, specific tests and the lack of significantly elevated serum muscle enzyme activities. Occasionally sedentary horses may present with classic signs of rhabdomyolysis with markedly elevated serum muscle enzyme activities. In these animals underlying genetic susceptibility, more usually associated with exertional forms of the disease, is possible because other events such as stress may precipitate attacks. Alternatively, other causes (such as atypical myopathy (acquired multiple acyl CoA deficiency) should be considered.

Management

In severe cases, exercise should be stopped and the horse rested in a deep-bedded stall. In mildly affected animals gentle hand walking is recommended.

Mildly affected animals, in which vital signs are close to normal can recover without intravenous fluid therapy, however they should be monitored for signs of deterioration. In moderate to more severe cases however, (even in those without pigmenturia), establishing diuresis and preventing or treating hypovolemia is the priority because myoglobin is nephrotoxic.

Large volumes of isotonic fluids are usually effective (0.9% NaCl or lactated Ringer's solution infused intravenously at 100 - 150 ml/kg/24 hours). The addition of sodium bicarbonate to fluids, though rarely necessary,[5] is generally only indicated in a horse with metabolic acidosis when the urine remains acidic despite fluid therapy, because myoglobin is significantly more nephrotoxic when in acidic urine.[6]

If there is little or no urine production during appropriate intravenous administration of fluids, attempts should be made to invoke diuresis. Furosemide is generally effective (0.5-1 mg/kg IV or IM BID). Careful monitoring and adjustment of fluid rates is essential to ensure that diuresis does not cause or exacerbate hypovolemia. Diuretics are not recommended in animals not receiving fluids. Absence of urination for several hours despite fluid therapy and furosemide, suggests oliguric renal failure, in which case renal blood flow may be increased with dopamine (3 – 5 µg/kg/minute diluted in 5% dextrose intravenously) to promote diuresis. Close monitoring of heart rate and the ECG are required because of the risk of tacchyarrhythmias.

In mild to moderate cases NSAIDs (e.g. phenylbutazone 4.4 mg/kg IV or PO Q 12 h for one day followed by 2.2 mg/kg PO Q 12 h for several days; or flunixin meglumine 0.5 - 1.1 mg/kg IV or PO Q12-24 h) medication is all that is necessary, however clinicians should monitor renal function given the drugs' nephrotoxicity. In severe cases more potent analgesics such as butorphanol (0.1 mg/kg IV or IM Q 4-6 hrs) may be required. In the worst cases the pain is very hard to manage.

Acepromazine (0.04 – 0.11 mg/kg IV or IM Q8 h has been advocated for its vasodilatory effects within the musculature, however it should be used with caution in the hypovolemic animal. Corticosteroids (e.g. dexamethasone (0.02 mg/kg IV SID for 1 to 2 days) are sometimes used to stabilize membranes, but their efficacy is unproven. Dantrolene, a

drug that limits release of Ca^{2+} from the sarcoplasmic reticulum via the skeletal muscle ryanodine receptor (RYR1)[7] has been used in the acute stages of idiopathic rhabdomyolysis.[8,9] This drug is sometimes used for prophylaxis (see below), however a dose of 2-3mg/kg per os QID may also be helpful in acute stages of disease.

Prognosis

The prognosis for most horses with mild to moderate acute episodes of ER is good for recovery, but horses with an underlying genetic susceptibility will always be prone to future episodes.
For horses in shock, the prognosis is poor. Many horses that develop acute renal failure, if treated early, recover.

INVESTIGATION AND PROPHYLAXIS (BETWEEN EPISODES)

Histories are often compatible with recurring episodes of rhabdomyolysis as described above. Often, a horse is presented because there is no good explanation for the rhabdomyolysis (and may be normal on examination) but owners believe that some underlying factor is responsible.
Some horses may present with histories of poor performance.[10]

Exercise testing

An exercise test may be helpful in horses with no evidence of ongoing muscle damage (by measuring serum CK and AST activities), but is potentially dangerous in ER-susceptible animals hence sound clinical judgment is critical. Exercise testing is contraindicated in animals with evidence of recent muscle damage. The sensitivity and specificity of exercise tests have not been evaluated, and the intermittent nature of the disease may result in a negative test in a susceptible animal. Ideally, a positive test should provoke a subclinical episode of rhabdomyolysis that can be detected via a rise in CK activity between pre and 4-hour post exercis e serum samples. Titrating the amount and type of exercise can be difficult, but should be based on the horse's history and level of fitness. Bouts of maximal exercise appear less likely to precipitate episodes[11,12] and are therefore not recommended.
Generally, 10 to 20 minutes of moderate exercise (trot and canter) on a lunge line or a treadmill is appropriate. Clinicians differ in their interpretation of the changes in plasma CK activity following exercise, and the degree of change likely reflects the underlying aetiology.

Electrolyte clearance ratios

Clearance ratios are calculated to assess whole body electrolyte status and have been advocated for assessment of exertional rhabdomyolysis cases. However , the identification of wide daily fluctuations in clearance ratios in the same horse, despite standardized management, casts doubt on the test's relevance.[14, 15]

Plasma vitamin E and selenium:

Most ER-susceptible horses are not deficient in vitamin E or selenium, but measuring plasma vitamin E and selenium concentrations may demonstrate deficiencies in animals on poor planes of nutrition or from selenium-deficient areas.

Muscle biopsy:

A muscle biopsy is often indicated in an animal with several unexplained episodes of ER. The biopsy site is based on the physical examination, but epaxial, gluteal and semimembranosus muscles are most commonly chosen. Ideally, a fresh muscle sample should be snap-frozen in isopentane cooled in liquid nitrogen, but since this is not usually practical, a compromise is necessary: good results can be obtained when a sample is sent overnight to a suitable laboratory, chilled (not frozen) on icepacks.[16]
Formalin-fixation, though more convenient, is unsuitable for histochemical investigation and leads to more artifact; it does allow morphological assessment however and has enabled a diagnosis to be reached in cases of polysaccharide storage myopathy (PSSM).

Muscle biopsy procedure:
(www.rvc.ac.uk/NeuroLab/)

Materials required
Drugs for sedation
Lignocaine 2% injection
Sterile gloves
Scalpel
Forcep
Small Gelpi retractor
Needle holders
Suture material / staples
Sterile gauze swabs
Screw top container x2
10% formalin (10-20 ml)
Ice packs
Polystyrene box
Card and pins

1. Contact the laboratory (+44 (0) 20 3214 8016) and organise same day or overnight courier service prior to sampling. Avoid shipping over the weekend.
2. For horses with exertional myopathies the semimembranosis is generally chosen. For other disorders, choose the site based on the most obviously affected muscle or biopsy several regions.
3. Sedate horse and prepare skin for sterile surgery.
4. A Bergstrom biopsy needle is suitable, but reliable (and sometimes better) results are obtained with open biopsy.
5. Inject subcutaneously up to 10 ml of local anaesthetic, taking care to avoid direct injection into the muscle layer.
6. Make a 4cm incision (in the same orientation as the muscle fibres) in the skin and subcutaneous tissue, exposing the underlying muscle belly. Separate with Gelpi retractor.
7. Make 2 parallel incisions (3 cm long) in the muscle parallel to the muscle fibres, about 0.6cm apart.
8. Then, while holding the incised muscle proximally, incise the proximal region and carefully undermine the strip (0.6 cm depth). Finally incise distally. The muscle will contract as it is incised. Take care not to damage the muscle sample.
9. Divide the muscle into 2 pieces. Pin one piece at either end onto card and place in 10% formalin in a screw top container.
10. Without damaging it, carefully place the other piece inside a small sterile plastic screw top container WITHOUT formalin. This fresh piece will be used for most analysis in the lab, so reserve the better half for this sample!
11. Close dead space completely and close subcutaneous layer. **Note: a thorough closure reduces chance of dehiscence.**
12. Suture or staple skin.
13. Place both containers in a polystyrene box containing ice packs. Take care not to place the containers directly against the icepacks (the muscle itself must not freeze). Instead, provide some insulation (e.g. cotton wool).
14. If possible, include 1 x 10ml blood in EDTA. These samples are stored frozen to allow DNA analysis if applicable.
15. Seal and post the box by courier or hand deliver.

GENETIC TESTING

Highly specific and sensitive testing is now available for certain genetic forms of exertional rhabdomyolysis, including type 1 polysaccharide storage myopathy (PSSM1) [17,18] and malignant hyperthermia. [19] Whole blood (in EDTA) or hair roots submitted to laboratories are suitable for genetic testing.

Prophylaxis and management

Diet:

Despite apparent differences in etiology and pathogenesis[20] the substitution of a proportion of dietary calories derived from soluble carbohydrate with additional fat, reduces the severity of episodes of ER via poorly understood mechanisms in both Thoroughbreds with dysfunctional calcium regulation [21] and horses with PSSM.[22]

High fat diets have a calming effect on horses[23] and are associated with lower plasma cortisol concentrations during exercise; [24] since

stress has been associated with ER in Thoroughbreds[25] and Standardbreds,[26] the calming effect may explain the rapid prophylactic efficacy of high fat diets in recurrent ER caused by abnormal calcium regulation. [21] Further work is required to clarify the attractive hypothesis that the beneficial effect of fat in PSSM is a shift of energy metabolism from the assumed dysfunctional glucose uptake/glycogen synthesis pathways, towards beta-oxidation.

Most studies have investigated the beneficial effect of a diet that contains approximately 20% fat, together with a reduction in soluble carbohydrate (grain) intake.[21] Increased fat in the diet can be achieved by the addition of vegetable oil (up to approximately 1g/kg bodyweight per day or 1.1ml/kg bodyweight per day). Rice bran (15-20% fat) can also be used as a substitute source in animals that find the oil unpalatable, or a combination may be suitable in some animals. Forage intake should be at least 1% of bodyweight, but fast growing lush pastures and high quality sweet hays should be avoided. Alfalfa pellets and beet pulp may also be used. Horses should be introduced to higher fat diets over several weeks and the dietary intake of minerals and vitamins should meet recommendations. In particular, owners should ensure that the calcium: phosphorous ratio in the diet is adequate, as rice bran and high fiber products such as beet pulp contain excessive phosphorous relative to calcium. There are several high fat, low soluble carbohydrate feeds commercially available.

Exercise:

Evidence suggests that a regular daily exercise program with changes introduced gradually, and preferably daily access to pasture, may help horses that are susceptible to recurrent episodes of ER.[22,25]

Electrolyte therapy:

Electrolyte supplementation is appropriate in animals that have been identified as deficient by specific testing. There is no rationale for the once popular administration of sodium bicarbonate to horses to prevent episodes, because most affected animals do not have underlying acid-base disorders prior to exercise and become alkalotic during exercise.[5, 21]

Antioxidant supplementation:

Vitamin E (1 - 6 IU/kg/day per day alpha-tocopherol) and selenium (1- 2 mg/day) supplementation in food are indicated when deficiencies have been confirmed.

Prophylaxis:

Numerous drugs are administered prophylactically, but most are used with unproven efficacy. The recent identification of separate disease etiologies may result in properly controlled drugs' trials in the near future. There is some published data and considerable anecdotal evidence, suggesting that oral dantrolene, administered 1-2 hours before exercise (2-3mg/kg per os) is highly effective in reducing severity or abolishing episodes completely.

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