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ATYPICAL MYOPATHY

Atypical myopathy

Atypical myopathy – previously named atypical myoglobinuria – was reported as an apparently new syndrome in 1984 (Votion, 2016). It was named atypical because, unlike exertional rhabdomyolysis syndromes, the affected horses were kept at grass with little supplementary feeding; it was not induced by exertion; and it had a high fatality rate. The name was changed from myoglobinuria – a clinical sign of the condition – to myopathy, to more correctly describe it.

In the USA, seasonal pasture myopathy is a very similar disease and it is likely that it has a common aetiology.

Outbreaks occurred sporadically in the autumn, but the condition has become more prevalent in Great Britain and Europe since 2000, and a smaller number of cases have also been observed in spring following large autumnal outbreaks (Galen et al, 2012a).

Atypical myopathy (AM) can affect individual horses or several horses in the same group. Youngsters – except young foals – are predominantly affected and horses over the age of 20 have also been found to be susceptible (Galen et al, 2012a). Before the causal agent was determined, research indicated that horses kept for more than six hours per day on overgrazed pasture with a large quantity of trees on or around it, and with dead leaves and dead wood, were at an increased risk (Galen et al, 2012b). The risk of AM was also increased when additional hay or haylage or supplementary feeds were not provided; although, in another study, supplementary hay on the ground in a humid environment increased the risk (Galen et al, 2008).

Certain weather conditions – such as little sunshine, cool temperatures, heavy rainfall and strong winds – were found to favour AM (Galen et al, 2008) and it was hypothesised that these weather conditions might be linked to wind and rain making the causal agent more accessible on the ground (Votion, 2016). Later the link to trees was investigated, and certain species found to be the causal agent.

Aetiology

Several possible causes were considered, including toxic products such as herbicides, weed killers and iodophores, phytotoxins, mycotoxins, *Clostridial* toxins, and selenium and vitamin E deficiency (Galen et al, 2008). Research indicated that a multiple acrylic-coenzyme A (CoA) dehydrogenase deficiency (MADD) was involved, which guided the research to find the aetiological toxin that caused this biochemical effect (Votion, 2016).

Research had linked an environmental agent, and when investigating the connection with trees, research into seasonal pasture myopathy (SPM) linked the disease to ingestion of seeds from the box elder tree, *Acer negundo* (Valberg et al, 2013). Box elder seeds contain the toxin hypoglycin A.

The hypoglcin A metabolite, methylenecyclopropyl acetic acid (MCPA) has been found in SPM horse serum and urine (Valberg et al, 2013) and in the serum of European horses with atypical myopathy (Votion et al, 2014). Lower serum concentrations of hypoglycin A have been found in apparently healthy co-grazing horses (Krageloh et al, 2018).

Figure 1. *Leaves and seeds on a sycamore tree* (Acer pseudoplatanus).

The sycamore tree (*Acer pseudoplatanus*) seeds, samaras (the winged seed, usually in a pair, at right angles) and seedlings have all been found to contain hypoglycin A (Baise et al, 2016) and are, therefore, the probable cause of atypical myopathy in the UK and Europe (**Figure 1**). Box elder, although not commonly found in Europe, has been the cause in one European case (Votion, 2016). The seeds are the likely cause of AM in the autumn, and seedlings the cause in the spring.

Hypoglycin A may be present in other *Acer* species or in the Sapindaceae family of trees (this includes the horse chestnut tree). Other trees and shrubs, including some that produce samaras, have been found around pastures associated with AM (Votion, 2016); and further research is required.

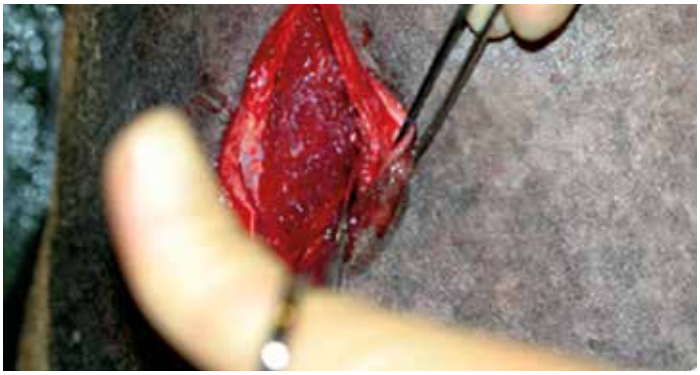

Figure 2. *Diagnosis may be based upon clinical examination, history, laboratory findings and muscle biopsy for histological analysis.*

Pathophysiology

It is proposed that intestinal absorption of hypoglycin A and its metabolism to MCPA conjugates is required for development of AM (Krageloh et al, 2018). Hypoglycin A causes the acquired multiple acyl-CoA dehydrogenase deficiency (MADD) seen in AM and SPM.

The effect of MADD results in an inhibition of various mitochondrial enzymes, leading to reduced beta-oxidation of fatty acids and accumulation of toxic acylcarnitines (Krageloh et al, 2018). MCPA-carnitine is then present in blood and MCPA-glycine is eliminated in urine (Votion, 2016). Because there is an inability to metabolise fatty acids – the main energy source of muscle – a rapid and widespread death of muscle cells occurs, as well as abnormal lipid storage.

This myodegenerative process of AM more selectively affects oxidative rather than glycolytic muscle fibres (Galen et al, 2008). These are slow twitch, Type 1 fibres, mainly found in postural and respiratory muscles, rather than the fast twitch, Type 2 fibres, found in locomotor muscles.

Clinical signs

The clinical signs are usually a sudden onset of severe general weakness, with muscular stiffness. Affected horses often become recumbent within a few hours and are sometimes found dead at pasture, with no evidence of premonitory signs (Galen et al, 2008). The latency period has been estimated to be at up to four days (Galen et al, 2012a), because cases have occurred in horses that had been stabled for up to four days before showing symptoms.

The signs that occur in more than 50 per cent of cases are (Votion, 2016):

- muscular weakness, stiffness and reluctance to move
- myoglobinuria
- lethargy, depression
- recumbency
- sweating (but normal body temperature)
- muscle tremors
- congested mucous membranes
- distended bladder on rectal palpation
- rapid deterioration of clinical signs.

Other signs that may be found include:

- dysphagia – may have signs of oesophageal choke and drop food and saliva from their mouths and nostrils; although an appetite may still be present
- dyspnoea
- tachycardia (usually mild), possible heart murmurs
- pain
- colic
- may be found dead.

Occasionally, other signs, such as gastrointestinal impaction, diarrhoea, penile prolapse, buccal ulceration and renal dysfunction may be observed (Galen et al, 2012a).

Prognostic indicators

Recumbency, sweating, anorexia, dyspnoea, tachypnoea and/or tachycardia have been associated with non-survival (Galen et al, 2012b). Normal arterial partial pressures of oxygen (PaO_2) levels were also associated with survival (Galen et al, 2008); as were remaining standing for most of the time, normothermia, normal mucous membranes, defaecation (Galen et al, 2012b).

In another study, initial creatinine kinase (CK) of >100,000 IU/L has been associated with increased mortality (Gonzalez-Medina et al, 2016). Abnormal rectal temperature, distended bladder on rectal palpation and higher heart rates were also associated with non-survival (Gonzalez-Medina et al, 2016).

Diagnosis

Diagnosis may be based upon clinical examination, history, laboratory findings and histology (**Figure 2**).

Laboratory findings

Blood samples will show elevated muscle enzymes – in particular creatinine kinase (CK). These levels peak after several hours, so samples taken early in the disease may not give a true indication of the extent of muscle damage. Usually in AM, CK levels are >10,000 IU/L.

CK may also be moderate when horses are recumbent owing to muscle compression and the CK not yet being released into the blood (Galen et al, 2008). On the other hand, the CK may be so high that it is not possible initially to determine the correct value without requesting that the sample be diluted.

Hypoglycin A concentration in blood can be useful for screening in suspected cases (Baise et al, 2016).

Metabolomic studies have shown acylcarnitines and glycine conjugates elevated in the serum and urine of affected horses; as well as organic and amino acids, purine, pyrimidine metabolites and vitamins and their degradation products (Karlikova et al, 2016). Serial monitoring of metabolic profiles demonstrated changes in acylcarnitines and glycine conjugates that indicted the progression or recovery from disease. The severity of metabolite changes reflected the severity of the disease (Karlikova et al, 2016).

Urine analysis may confirm the presence of myoglobin; and muscle biopsy can confirm degeneration and necrosis in fibres (Type 1) in postural and respiratory muscles.

Post-mortem findings may be the lack of other evident causes of death, and no gross lesions. There may be discolourations in postural, respiratory and cardiac muscles.

Treatment

Mortality rates have been reported at 74 per cent and, although there is no cure, treatment significantly increases the survival rate (Galen et al, 2012a). The aims of treatment (Votion 2016) are to:

- minimise further muscle damage
- restore circulating volumes
- correct acid-base and electrolyte disturbances
- provide energy to muscle cells that they are still able to utilise – as carbohydrate rather than lipid metabolism
- provide vitamins and antioxidants
- provide pain relief, if present.

Hospitalisation

Supportive treatment is best provided by intensive nursing in a veterinary hospital environment (**Figure 3**). Fluid therapy reverses

Figure 3. *Supportive treatment is best provided by intensive nursing in a veterinary hospital environment.*

dehydration, protects kidneys from the damage circulating myoglobin may cause and can help to correct electrolyte disturbances (**Figure 4**).

Pain relief may be in the form of NSAIDs, opioids or a lidocaine infusion. The latter can reduce pain as well as having anti-inflammatory and anti-oxidant benefits. It may also reduce life-threatening heart dysrhythmia. Use of NSAIDs should be undertaken with care, owing to their potential renal toxicity. Hydration must be maintained; and renal indices – such as BUN, creatinine and urinalysis – should be monitored (Galen et al, 2008).

Intravenous administration of glucose, oral glucose, insulin, heparin and chromium supplementation has been used to enhance carbohydrate metabolism and manage hyperlipaemia, hyperglycaemia and improve insulin sensitivity (Galen et al, 2008).

Feeding a high quantity of carbohydrates may be beneficial. If difficulty with urination is encountered, bladder catheterisation may be required.

Treatment with vitamins and antioxidants has been associated with survival (Galen et al, 2012b; Gonzalez-Medina et al, 2016). Vitamins B, C and E, and selenium may have a protective role as anti-oxidants – against a potential oxidative stress encountered in the pathophysiological process of AM. Vitamin B_2 may improve mitochondrial metabolism (Votion, 2016) and carnitine may also be beneficial.

Severe hypoxia can develop and nasal oxygen may be indicated. Sternal – rather than lateral – recumbency should be employed, to decrease any further muscle and pulmonary compression; and stress should be minimised.

Dantrolene sodium has been given as a treatment, in an attempt to limit rhabdomyolysis (Galen et al, 2008). Euthanasia may be a preferred option when there is a poor prognosis.

Survivors recover within a range of one to 30 days – usually after around 10 days (+/- approximately five days) (Galen et al, 2012a). The majority of non-survivors died or were euthanised within 72 hours, and all within 10 days (Galen et al, 2012a).

Preventive therapy

Co-grazing horses may be affected sub-clinically or clinically. The recommended management should be to remove the horses from the pasture to stables, to monitor closely for signs of AM and to monitor CK levels in blood (Galen et al, 2008).

A recent study has shown activated charcoal composites – containing activated charcoal, kaolin, silicon dioxide and oak bark – and activated charcoal, to be potent binding substances for hypoglycin A and, therefore, possibly useful to reduce intestinal absorption (Krageloh et al, 2018). Activated charcoal may be useful in the treatment of horses in early stages of intoxication and as a preventive measure in co-grazers of AM-affected horses.

Figure 4. *Fluid therapy reverses dehydration, protects kidneys from the damage circulating myoglobin may cause and can help to correct electrolyte disturbances (Photo: Hazel Clewley).*

Pasture management

There is a series of common sense measures that should be considered:

- avoiding pastures with sycamore trees on the pasture or close by
- turning out for short periods each day (<6hrs)
- regularly inspecting pastures for sycamore seeds that may have been blown onto pasture and picking them up
- fencing off areas where sycamore tree seeds have fallen
- removing sycamore seedlings
- supplying extra hay or haylage when pasture quality is poor
- reducing stocking levels so as to ensure enough good pasture for each horse
- managing pasture turn-out at times, depending on weather conditions.

Continuing research

It is not clear why the number of AM outbreaks has increased of late, despite the long establishment of sycamore trees in the UK, It is possible that climate changes have contributed (Galen et al, 2008) and outbreak triggers are multifactorial.

The atypical myopathy alert group (AMAG) was set up as an informal European epidemio-surveillience network (Galen et al, 2012b). The AMAG has collected data and continues to gather information about outbreaks. It can alert veterinary professionals and owners to outbreaks via the atypical myopathy website (Votion, 2016).

Areas of continuing research include (Votion 2016):

- the environmental conditions that are responsible for the emergence of disease
- what affects the toxicity of the *Acer* species (and other trees) – increased production of samaras, for example; maturation-dormancy stages, including the hypothesis that unripe seeds contain higher levels of toxic hypoglycin A; heat, moisture and cold
- risk-based prevention
- improving case management – diagnosis, prognosis assessment, preventive measures and curative treatments. ■

PPD Questions

1. What is the toxin that causes seasonal atypical myopathy?
A. hypoglycin A
B. hypoglycin S
C. high glycogen
D. hydrogenase A.

2. Which tree is associated with seasonal atypical myopathy (AM) in the UK ?
A. box elder
B. oak
C. sycamore
D. chestnut.

3. An acquired deficiency is caused in AM. Which is it ?
A. multiple acetylene deficiency disorder (MADD)
B. multiple acyl-CoA dehydrogenase deficiency (MADD)
C. methyl acetylene dehydrogenase deficiency (MADD)
D. methyl acyl-CoA dehydrogenase deficiency (MADD).

4. Which is not usually a clinical sign of AM?
A. stiffness
B. recumbency
C. muscle tremors
D. absence of gut sounds.

5. The survival rate for AM is approximately:
A. 24 per cent
B. 34 per cent
C. 54 per cent
D. 76 per cent.

Answers
1.A 2.C (box elder is associated with SPM in the USA) 3.B 4.D 5.A.

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