Equine hypoglycin toxicity

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Atypical myopathy is a disease that has risen to prominence recently as greater numbers of cases have been diagnosed. Anecdotally, there appears to be a genuine increase in incidence; however, this may be the result of greater awareness among vets and horse owners.

Figure 1. The common sycamore, *Acer pseudoplatanus*.

The increase in case reports – and, hence, interest – has been associated with increased understanding of the disease. It is now appreciated European atypical myopathy and US seasonal pasture myopathy are the same conditions and, as they are no longer “atypical”, this description seems outdated.

The term “sycamore poisoning” is simple to understand, but other potential sources of toxicity exist. Previous names have included atypical myoglobinuria and (erroneously) white snakeroot toxicosis.

Pathogenesis

In 2008, Westermann et al[1] demonstrated atypical myopathy was associated with multiple acyl-CoA dehydrogenase deficiency (MADD)[1] and impairment of mitochondrial aerobic metabolism. Similarities between MADD in horses and people were identified, providing an essential clue to the

cause of the disease.

An acquired MADD condition, called Jamaican vomiting sickness, is triggered by the ingestion of hypoglycin A in ackee fruit and existing botanical studies provided a clue as to probable sources of hypoglycin A in an equine environment[2].

In the US, presence of hypoglycin A was confirmed in seeds from box elder (*Acer negundo*) trees collected at outbreaks of atypical myopathy[3]. In Europe, the presence of high concentrations of methylene cyclopropyl acetic acid-carnitine in serum from horses with atypical myopathy, but not controls, again indicated hypoglycin A toxicity.

A case report from Germany last year provided further evidence ingestion of sycamore seeds containing hypoglycin A was the cause of disease[4]; an affected horse had fragments of sycamore seeds in its stomach, acute rhabdomyolysis of type one muscles, accumulation of lipid within affected cells and increased urine and serum concentrations of several acylcarnitines, acylglycines and metabolites of hypoglycin A.

Hypoglycin A levels in blood and urine can discriminate between affected and unaffected horses[5]. Sycamore seedlings, as well as seeds, have subsequently been identified as potential sources of hypoglycin A[6].

Hypoglycin A is metabolised to methylene cyclopropyl acetic acid within the mitochondria of the muscle cell, where it exerts two effects:

- It irreversibly inhibits medium and short acyl-CoA dehydrogenases inhibiting the oxidation of fatty acids (and, hence, production of energy) within the mitochondria.
- It disrupts the carnitine-acyl-CoA transferase system impairing the transport of long-chain fatty acids into the mitochondrion. Type one muscle fibres – which predominate in cardiac, respiratory and postural muscles – are more dependent on fatty acid oxidation than type two fibres and are, therefore, more severely affected.

There is, therefore, a considerable body of evidence atypical myopathy is hypoglycin toxicity. Now the condition is better defined and no longer “atypical”, the term hypoglycin toxicity would seem more appropriate.

Potential sources of hypoglycin A

Exhaustive studies have not been performed; however, to date, the disease has only been identified in association with exposure to seeds of either the common sycamore (*Acer pseudoplatanus*; **Figure 1**) in Europe or the box elder in the US.

All European cases have been associated with the common sycamore. Other members of the

Sapindaceae family of trees, which include acers (maples), may produce the toxin, but the common sycamore is the only one horses are likely to come into contact with in the UK.

Figure 2. Seeds (or samaras) from *Acer pseudoplatanus*.

Some ornamental acer species found in parks and gardens produce seeds that contain the toxin – for example, the Japanese maple (*Acer palmatum*), silver maple (*Acer saccharinum*), mountain maple (*Acer spicatum*) and sugar maple (*Acer saccharum*)[2]. Fortunately, the field maple (*Acer campestre*), which is found commonly in hedgerows, and the Norway maple (*Acer platanoides*), which is grown as an ornamental tree in the UK, do not produce the toxin[2,7].

Extrapolating from the known toxic dose of hypoglycin A in rats, it has been estimated ingestion of 26.5mg of hypoglycin A would be required to cause toxicity in a 500kg horse. The amount of hypoglycin in sycamore seeds (also known as samaras; **Figure 2**) varies markedly and may range from 0.7?g/seed to 821?g/seed[3,5,8].

Ingestion of anywhere between 32 seeds and 9,000 seeds may, therefore, be required to cause disease. Susceptibility to disease is likely to differ considerably between individuals; indeed, Baise et al[6] estimated an asymptomatic horse had ingested 46mg of hypoglycin and suggested there may be additional factors involved in the development of disease.

The stage of the seeds' development does not appear to be relevant to hypoglycin concentration and marked variation exists in the concentration of toxin between seeds from the same tree. Climatic factors and tree stress (which may also be caused by climate) may affect the concentration of hypoglycin within seeds and contribute to the sporadic nature of the disease.

Climatic factors will also affect seed dispersal. Baise et al[6] demonstrated hypoglycin A is present in sycamore seedlings (**Figure 3**), as well as seeds, but not present in fallen sycamore leaves.

Risk factors for disease

Risk factors for disease were investigated in cases reported to the atypical myopathy alert group between 2006 and 2009[9]. Most factors identified were related to the presence of trees – trees on or around the pasture, fallen leaves, fallen dead wood and sparse pasture; however, sloping ground was also identified as a risk factor.

Figure 3. A seedling of *Acer pseudoplatanus*.

In previous studies, absence of sunshine[10] and stormy or windy weather[3,10,11] were associated with the development of disease, presumably because this resulted in greater seed dispersal. Cases reduce after the first frosts, which may just be a reflection of the changing season and reduced exposure to seeds, rather than the frost per se, as hypoglycin A is not destroyed by freezing.

Horse factors, in the study of cases reported to the atypical myopathy alert group between 2006 and 2009, included age, with most affected animals being young adults. Increased access to pasture was a factor, with affected horses spending more than six hours per day at pasture and 86 per cent being turned out 24/7.

Two per cent of horses were stabled at the time of disease, but for a maximum of four days prior to disease onset, suggesting there can be a latent period of four days or more between exposure and disease in some cases. Neither breed nor gender were identified as risk factors. Horses in good body condition were more likely to develop the disease, but horses of all body conditions were affected[9].

The majority of cases of hypoglycin toxicity occur in autumn (93 per cent in the study by van Galen et al[9]), but small numbers of cases occur year-round.

Although there was no clear peak in cases in spring in the study by van Galen et al[9], it is well

recognised the risk of disease increases in spring compared to winter and summer. These cases also occur on pasture where sycamores are present and sycamore seedlings are assumed to be the source of hypoglycin[6].

It has been speculated the apparent increase in cases of hypoglycin toxicity may be related to more horses having restricted access to grazing – either as a result of increased awareness of the risks of obesity and laminitis, or because increasing numbers of horses are kept on yards with a high stocking density.

Clinical findings and diagnosis

Early signs, such as reluctance to work and a quiet demeanour, may be reported a few days before the more severe signs of myopathy develop and should ring alarm bells in horses at risk. The occurrence of mild signs associated with work may initially be mistaken for exertional myopathy rather than hypoglycin toxicity.

Most of the clinical signs of hypoglycin toxicity relate to muscle weakness (stiffness, tremors, reluctance to move, lethargy, low head carriage and dysphagia) or pain (sweating, depression and gastrointestinal impactions).

If the respiratory muscles are severely affected then the horse may exhibit rapid shallow breathing. Tachycardia may occur as a result of cardiomyopathy and/or pain. Arrhythmias are another indication of cardiomyopathy. Death may occur as a result of cardiac or, more commonly, respiratory failure.

Figure 4. Dark red/brown urine from a horse with atypical myopathy. Pigmenturia is the most reliable sign of the disease.

Pigmenturia (**Figure 4**) occurs in more than 90 per cent of cases and can be used to differentiate hypoglycin toxicity from other differential diagnoses, such as colic, grass sickness or even laminitis.

If there is any suspicion of hypoglycin toxicity then a urinary catheter should be passed and urine collected. As other causes of pigmenturia are rare, the presence of red/brown urine in a horse with other signs of hypoglycin toxicity effectively confirms the diagnosis.

Hypoglycin toxicity has been mistaken for surgical colic and affected cases have been subjected to exploratory laparotomy unnecessarily, so passage of a urinary catheter should be considered prior to emergency laparotomy if risk factors exist for hypoglycin toxicity and any doubt exists over the existence of an intra-abdominal lesion.

Secondary complications are common and may include:

- head oedema
- pressure sores
- buccal ulceration/necrosis
- gastric ulceration
- choke
- impactions

- diarrhoea
- renal dysfunction
- paraphimosis
- corneal ulcers

Laboratory data

Muscle enzymes will demonstrate the presence of a myopathy, but are not always increased at the onset of clinical signs. Creatine kinase should be the first muscle enzyme to increase and may reach levels of up to 7,000,000U/L within hours or days of the onset of myopathy. Other laboratory changes include erythrocytosis, hyperlactataemia, azotaemia, neutrophilia and hyperglycaemia, and can be explained by hypovolaemia, adrenergic stimulation and stress. Inappetence and negative energy balance may result in hyperlipaemia.

Cardiac troponin may increase if cardiomyopathy is present. Mild increases in acute phase proteins and liver enzymes may also develop.

Definitive diagnosis

Hypoglycin toxicity can be definitively diagnosed by collection of a type one muscle biopsy (generally, intercostalis or sacrocaudalis dorsalis muscles) or measurement of toxic metabolites in blood or urine.

Measurement of hypoglycin A and acylcarnitine concentrations is not available commercially, but samples can be submitted to the RVC Comparative Neuromuscular Diseases Laboratory as part of its ongoing research (for more information, email sgonzalezmedina@rvc.ac.uk).

Prognosis

Hypoglycin toxicity carries a poor prognosis. Survival rates vary from 3 per cent to 57 per cent, with the largest study of 354 cases between 2006 and 2009 reporting 26 per cent survival[12]. There are issues with bias with all studies, as cases that are more severe or referred are more likely to be reported. Factors that have been identified as influencing prognosis are listed in **Table 1**.

Predicting the level of intervention required in hypoglycin toxicity and the prognosis for survival is notoriously difficult and treatment should, therefore, be aggressive and proactive from the outset.

Often cases will clinically deteriorate over 48 hours and 72 hours before starting to improve (if they improve) and it is therefore worth considering hospitalisation as soon as hypoglycin toxicity is identified – and while transport is possible.

If affected animals make it past four days or five days from the onset of clinical signs then

prognosis improves markedly. Although long-term follow-up data is lacking, there appears to be no lasting effects of hypoglycin toxicity; if affected animals survive, they will return to their previous level of health and athletic activity.

Treatment

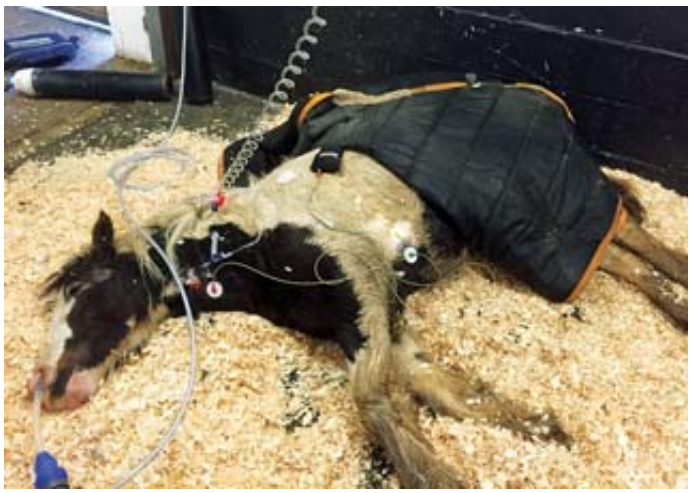

Figure 5. Constant rate infusions are an effective means of providing multimodal analgesia and offer significant advantages over intermittent administration of drug boluses.

Given the guarded prognosis, treatment is not for the faint-hearted and requires a large team to cope with the physical and emotional demands of nursing more severely affected animals (**Figure 5**).

If finances permit, even apparently mild cases benefit from transport to a suitably equipped and well-staffed hospital facility immediately before they potentially deteriorate. Transporting horses recumbent may be necessary and, although prognosis is poor, these horses can survive. Transportation lying down may even be preferable as it reduces the demands on postural muscles.

Analgesia

Some cases appear to be in extreme pain, while others just appear weak, and analgesia has to be determined on a case-by-case basis, with a default of administering too much analgesia rather than too little. Fluid therapy will be important in preventing potential nephrotoxic effects of NSAIDs in horses that are hypovolaemic. Options and doses for analgesia are listed in **Table 2**.

Constant rate infusions allow for more consistent and safer analgesia (**Figure 6**). The author will frequently use all the medications listed in **Table 1** concurrently, with the exception of butorphanol, which, being a partial opioid agonist, would only be used if morphine was unavailable.

Fluid therapy

Table 1. Factors that may affect prognosis in horses with hypoglycin toxicity[12-14]

Negative prognostic indicators	Neutral indicators	Positive prognostic indicators
• Recumbency • Sweating • Anorexia • Dyspnoea • Tachycardia • Tachypnoea • High PCV • Hypochloraemia • Hypoxaemia (<60mmHg) • Respiratory acidosis • Acylcarnitine profile	• Creatine kinase • Cardiac troponin • Hypoglycin A levels	• Remaining standing • Normothermia • Normal mucous membranes • Passage of faeces • Reducing creatine kinase levels

Table 1. Factors that may affect prognosis in horses with hypoglycin toxicity[12-14].

Fluid therapy is likely to be indicated to compensate for reduced voluntary intake, to correct hypovolaemia and promote diureses to protect against nephropathy caused by reduced renal blood flow and accumulation of myoglobin. Fluid replacement needs to be judicious, as rapid administration of high rates of IV fluids to a horse with compromised myocardial function may be deleterious.

Fluid requirements have to be calculated on a case-by-case basis and constantly reviewed. Hartmann's solution will replace the deficits in sodium and chloride, which often occur, and additional calcium supplementation may be warranted in some cases. Hyperkalaemia may occur as a result of muscle damage, but will correct with rehydration and does not require specific therapy.

Nutrition

Horses with hypoglycin toxicity will have a tendency to develop hyperlipaemia and hyperglycaemia as a result of stress, catabolism, impaired lipid metabolism, dependence on carbohydrate metabolism and increased hepatic gluconeogenesis. The diet should be low in fat and based on fibre with sufficient cereals and fruit or vegetables to meet requirements.

Nutritional requirements of these cases are unknown and probably vary markedly. It is therefore safest to aim to provide normal requirements for maintenance.

Feed should be made available little and often to avoid large fluctuations in glucose concentrations. Plasma glucose concentrations would ideally be monitored every four hours to six hours and triglyceride levels checked daily.

Most cases retain an appetite and loss of appetite is a poor prognostic indicator. Human contact and provision of a varied diet may help encourage eating. If assisted nutrition is required then it may be performed by means of soaked or liquid diets administered via nasogastric tube. Meeting requirements via this route is challenging and frequently impractical.

A better, though more expensive, alternative is to use a constant rate intravenous infusion of glucose and amino acids.

Frequently, concurrent insulin infusion will be required to maintain plasma glucose at an acceptable level (less than 10mmol/L). If finances permit, the author will instigate parenteral nutrition early in the hope it limits the damage to myocytes, which occurs as a result of mitochondrial dysfunction and reduced energy substrates.

In a study of prognostic factors, the only treatment to have a positive effect on outcome was supplementation with vitamins and/or antioxidants[12] as outlined in **Table 3**. Many clinicians also administer an amino acid supplement, such as Equitop Myoplast, to affected and recovering cases in the hope this improves muscle repair; however, there is no evidence it is efficacious.

Cardiorespiratory support

Respiratory function may be severely challenged, not only as a result of respiratory muscle weakness, but also as a result of:

- ventilation/perfusion ratio mismatch associated with recumbency
- upper respiratory tract oedema
- secondary aspiration pneumonia

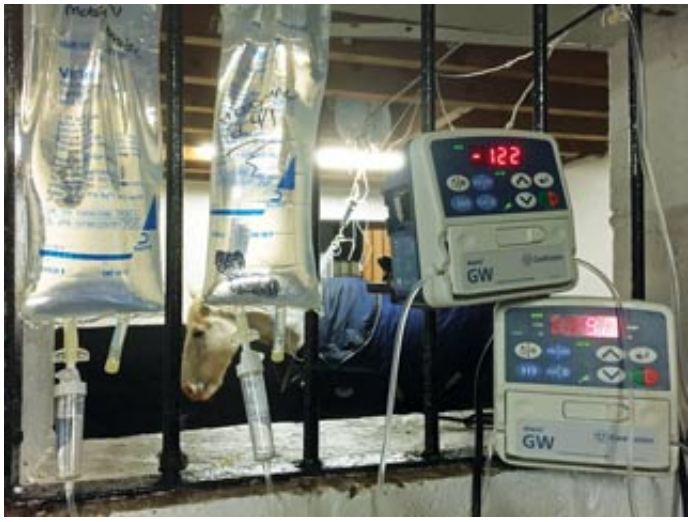

Figure 6. Constant rate infusion is an invaluable means of providing analgesia to horses with atypical myopathy.

Sternal recumbency is preferable to lateral and recumbent horses should be moved and/or turned every two hours to avoid pressure sores and compartment syndrome. To prevent oedema, the head should be kept elevated in standing patients that might otherwise be too weak to maintain it in a normal position.

Intranasal oxygen may be beneficial at flow rates of up to 10L/min. Antimicrobials may be indicated if there is a suspicion of aspiration pneumonia and acute phase proteins can be monitored to detect early signs of bacterial infection. Centrally acting respiratory stimulants, such as caffeine and doxapram, are of no benefit.

Myocardial dysfunction is common and may be demonstrated by persistent tachycardia, electrocardiographic changes or increased cardiac troponin. Telemetric electrocardiography provides a straightforward and non-invasive means of monitoring cardiac function.

If ventricular premature complexes are frequent, or there is ventricular tachycardia, the administration of lidocaine (1.3mg/kg, then CRI 0.05mg/kg/min) or magnesium sulphate (25mg/kg to 50mg/kg, then 5mg/kg/h to 20mg/kg/h) may be indicated. Negative inotropic drugs should be avoided.

Muscle relaxants

Use of muscle relaxants is controversial as they may just potentiate weakness. Acepromazine should be avoided in the presence of hypovolaemia, but may be considered in adequately hydrated patients. Magnesium sulphate and diazepam are alternatives. Methocarbamol is potentially nephrotoxic and should, therefore, be used with caution.

Dantrolene is contraindicated as it will inhibit mitochondrial function. Massage of affected muscles may ease pain, stimulate blood flow and have psychological benefits, so it is probably superior to any pharmaceutical agents for muscle relaxation.

Supportive care

Intensive nursing care and attention to the detail of other body systems that may be affected secondarily are paramount. Affected horses appear to respond positively to human contact and one-to-one nursing may not only be necessary logistically, but may also be therapeutic.

Additional to all the aforementioned specific treatments and monitoring measures, regular tasks may include:

- cleaning and lubrication of the eyes to prevent ulceration
- catheterisation of the bladder in the event of incontinence
- administration of laxatives and gastroprotectants

- prevention and management of pressure sores
- head elevation maintenance
- slinging of the penis to manage paraphimosis

Prevention

Table 2. Options for analgesia in horses with hypoglycin toxicity

Drug	Dose/route/frequency
Flunixin	1.1mg/kg IV bid
Morphine	0.1mg/kg to 0.3mg/kg IM q4-6h Initial IM bolus, then 0.05mg/kg/hr to 0.1mg/kg/hr CRI
Butorphanol	13µg/kg/hr IV
Lidocaine	1.3mg/kg bolus, then 0.05mg/kg/min CRI
Ketamine	0.2mg/kg to 0.8mg/kg IV 6.7µg/kg/min to 13.3µg/kg/min CRI

CRI: constant rate infusion.

Table 2. Options for analgesia in horses with hypoglycin toxicity.

Advice for owners who have sycamores on their property is as follows:

- Fence off areas where sycamore seeds are likely to fall. Expect seeds to travel up to three times the height of the tree and up to 100m in distance in severe weather[6].
- Regularly check when and where seeds are falling.
- Only turn horses out for a few hours each day and keep younger horses furthest away from sycamores.
- Provide extra forage during high-risk periods – especially where grazing is limited.
- Avoid feeding fats or oils during risk periods or if disease is suspected.
- Reduce stocking density around risk periods so there is ample grazing for every horse.
- Hypoglycin is water soluble. Ensure horses have access to fresh drinking water and are not drinking from streams or ponds under trees or are grazing marshy areas.
- Provide access to a vitamin/mineral supplement and salt block.
- Ensure worming is kept up to date.

The effect of mowing to collect seeds or destroy seedlings is unknown. As long as the action of mowing removes material from the pasture, it would seem to be a sensible precaution; however, it may risk reducing grass length providing greater access to seeds or leave toxic seedlings lying on the pasture. It is not known how long it takes for hypoglycin to degrade in field conditions.

The implementation of the measures mentioned has to be balanced against the potential for overfeeding horses at risk of laminitis and/or are suffering from equine metabolic syndrome or pituitary pars intermedia dysfunction.

Hypoglycin toxicity remains uncommon and it is easy for owners to lose perspective of the considerably greater risks posed by other more common diseases.

Clinical cases

Table 3. Supplements that may be beneficial to horses with hypoglycin toxicity[15,16]

Supplement	Dose	Route/ frequency	Reason
Vitamin E	5,000 international units	PO sid	Antioxidant
Selenium	1mg	PO sid	Antioxidant
Vitamin B	>12mg/day	IM/IV	Energy substrate
Carnitine	100mg/kg	PO sid	Promote lipid metabolism
Vitamin C	5,000mg-15,000mg	Infusion bid	Antioxidant

Table 3. Supplements that may be beneficial to horses with hypoglycin toxicity[15,16].

Clinical cases are often the tip of the proverbial iceberg; the majority of cohorts are likely to have ingested toxin and will be at increased risk of disease[7].

Outbreaks are common and a proactive approach is indicated to attempt to reduce the risk, or at least the severity, of further cases. The author suggests the following protocol is implemented where possible. In response to a case of hypoglycin toxicity:

- Remove all horses from affected pasture, prioritising the youngest horses.
- Provide a fat-free diet.
- Stable horses (preferably) or monitor them closely on “clean” paddocks for five days.
- Check aspartate aminotransferase (AST) and creatine phosphokinase (CK) concentrations on all horses at potential risk at the initial visit.
- Recheck AST and CK concentrations daily or every other day for five days.
- Consider providing vitamin/mineral supplementation as discussed beforehand.

If the at-risk horses become dull or have high muscle enzymes:

- Consider moving them to a hospital immediately for further investigation and treatment.
- Obtain a urine sample or catheterise the bladder to check for pigmenturia.
- Provide vitamin/mineral supplementation.

If pigmenturia or other clinical signs develop in at-risk horses, advise transport to a hospital immediately for intensive treatment. If hospitalisation is not a viable option then decide and

continually reassess whether treatment at home is feasible and ethical.

Contributing to research into hypoglycin toxicity

When faced with hypoglycin toxicity cases, consider contributing to future research into the condition by:

- Reporting cases
- Submitting samples of sycamore seeds, leaves and surplus ethylenediaminetetraacetic acid/heparin/serum blood samples to the RVC Comparative Neuromuscular Disease Laboratory – email sgonzalezmedina@rvc.ac.uk
- **Some drugs in this article are used under the cascade.**

References

1. Westermann CM, Dorland L, Votion DM, de Sain-van der Velden MG, Wijnberg ID, Wanders RJ, Spliet WG, Testerink N, Berger R, Ruiter JP and van der Kolk JH. (2008). Acquired multiple Acyl-CoA dehydrogenase deficiency in 10 horses with atypical myopathy, *Neuromusc Dis* **18**(5): 355-364.
2. Fowden L and Pratt HM (1973). Cyclopropylamino acids of the genus *Acer*: distribution and biosynthesis, *Phytochemistry* **12**(7): 1,677-1,681.
3. Valberg SJ, Sponseller BT, Hegeman AD, Earing J, Bender JB, Martinson KL, Patterson SE and Sweetman L (2013). Seasonal pasture myopathy/atypical myopathy in North America associated with ingestion of hypoglycin A within seeds of the box elder tree, *Equine Vet J* **45**(4): 419-426.
4. ?uraw A, Dietert K, Kühnel S, Sander J and Klopfleisch R (2015). Equine atypical myopathy caused by hypoglycin A intoxication associated with ingestion of sycamore maple tree seeds, *Equine Vet J* [Epub ahead of print].
5. Bochnia M, Ziegler J, Sander J, Uhlig A, Schaefer S, Vollstedt S, Glatter M, Abel S, Recknagel S, Schusser GF, Wensch-Dorendorf M and Zeyner A (2015). Hypoglycin A content in blood and urine discriminates horses with atypical myopathy from clinically normal horses grazing on the same pasture, *PLoS One* **10**(9): e0136785.
6. Baise E, Habyarimana JA, Amory H, Boemer F, Douny C, Gustin P, Marcillaud-Pitel C, Patarin F, Weber M and Votion DM (2015). Samaras and seedlings of *Acer pseudoplatanus* are potential sources of hypoglycin A intoxication in atypical myopathy without necessarily inducing clinical signs, *Equine Vet J* [Epub ahead of print].
7. Gröndahl G, Berglund A, Skidell J, Bondesson U and Salomonsson M (2015). Clinical research abstracts of the British Equine Veterinary Association Congress 2015, *Equine Vet J* **47**(Suppl 48): 22.
8. Unger L, Nicholson A, Jewitt EM, Gerber V, Hegeman A, Sweetman L and Valberg S (2014). Hypoglycin A concentrations in seeds of *Acer pseudoplatanus* trees growing on atypical myopathy-affected and control pastures, *J Vet Int Med* **28**(4): 1,289-1,293.

9. van Galen G, Marcillaud Pitel C, Saegerman C, Patarin F, Amory H, Baily JD, Cassart D, Gerber V, Hahn C, Harris P, Keen JA, Kirschvink N, Lefere L, McGorum B, Muller JM, Picavet MT, Piercy RJ, Roscher K, Serteyn D, Unger L, van der Kolk JH, van Loon G, Verwilghen D, Westermann CM and Votion DM (2012). European outbreaks of atypical myopathy in grazing equids (2006-2009): spatiotemporal distribution, history and clinical features, *Equine Vet J* **44**(5): 614-620.
10. Votion DM, Linden A, Saegerman C, Engels P, Erpicum M, Thiry E, Delguste C, Rouxhet S, Demoulin V, Navet R, Sluse F, Serteyn D, van Galen G and Amory H (2007). History and clinical features of atypical myopathy in horses in Belgium (2000-2005), *J Vet Intern Med* **21**(6): 1,380-1,391.
11. Finno CJ, Valberg SJ, Wünschmann A and Murphy MJ (2006). Seasonal pasture myopathy in horses in the midwestern United States: 14 cases (1998-2005), *J Am Vet Med Assoc* **229**(7): 1,134-1,141.
12. van Galen G, Saegerman C, Marcillaud Pitel C, Patarin F, Amory H, Baily JD, Cassart D, Gerber V, Hahn C, Harris P, Keen JA, Kirschvink N, Lefere L, McGorum B, Muller JM, Picavet MT, Piercy RJ, Roscher K, Serteyn D, Unger L, van der Kolk JH, van Loon G, Verwilghen D, Westermann CM and Votion DM (2012). European outbreaks of atypical myopathy in grazing horses (2006-2009): determination of indicators for risk and prognostic factors, *Equine Vet J* **44**(5): 621-625.
13. Verheyen T, Decloedt A, Clercq D and van Loon G (2012). Cardiac changes in horses with atypical myopathy, *J Vet Intern Med* **26**(4): 1,019–1,026.
14. Votion DM (2016). Personal communication.
15. van Galen G and Votion DM (2012). Management of cases suffering from atypical myopathy: interpretations of descriptive, epidemiological and pathophysiological findings. Part 1: first aid, cardiovascular, nutritional and digestive care, *Equine Vet Ed* **25**(5): 264-270.
16. van Galen G and Votion DM (2012). Management of cases suffering from atypical myopathy: interpretations of descriptive, epidemiological and pathophysiological findings. Part 2: muscular, urinary, respiratory and hepatic care, and inflammatory/infectious status, *Equine Vet Ed* **25**(6): 308-314.