By Rob Pilsworth MRCVS

Atypical myopathy update

Though rare in thoroughbreds thanks to the racing and breeding industry's sophisticated approach to feeding stock, this disease is often fatal and can strike quickly, usually in autumn when sycamore samaras are on the ground

Some years ago a friend telephoned us one evening for advice on treatment of a pony, which she thought had laminitis. It had been a long dry summer, and the weather had suddenly changed, with storms and heavy rain, often the combination of events which trigger an autumn flush of grass, and late-season laminitis. The symptoms were typical of laminitis – the pony was unwilling to move, dull, and appeared stiff, but then the friend added, 'Oh, and the other thing is, his urine is dark red'.

My heart sank, as this immediately made the most likely diagnosis that of Atypical Myopathy, a disease which has a mortality rate of 75% or more. The pony was immediately hospitalised, underwent intensive treatment, and survived, but most don't. So what is this disease and why has it suddenly become an emerging problem?

MARK HILLYER, NEH

Figure 1 A horse affected with Atypical Myoglobinurea undergoing treatment at Newmarket Equine Hospital. Note the wide-based stance, and drooping head, reflecting weakness in the postural muscles, the result of 'starvation' of their cells by the toxin Hypoglycin A. Following intensive treatment this horse made a full recovery

Early beginnings

The first recorded case series of this apparently new disease was published in the *Veterinary Record*, the 'trade mag' of the British Veterinary Association, in 1984 by the eminent Scottish veterinary scientist Karl Linklater. Going back over the years, however, it's clear that this disease had previously been seen sporadically, where it was named Myoglobinuria, because of the classic, though not universally present symptom, of intense staining of the urine red/brown with myoglobin.

Myoglobin is the pigment present in muscle tissue, the equivalent of haemoglobin in our blood, and is there to draw and store oxygen from the blood stream. When muscle cells burst, they release myoglobin into the bloodstream and this is then voided in the urine, leading to characteristic dark staining. Odd cases of this in horses at grass had been reported in the 1940s, in Canada in the 1960s, and in France in 1976, but numbers were small, and the emergence of a new disease syndrome wasn't recognised.

Following Linklater's report, increasing awareness and concern over the apparent increase in numbers of this disease made people sit up. Atypical Myoglobinuria became renamed as Atypical Myopathy, which more accurately reflects the nature of the illness, and the number of fatalities mounted. Finally, an outbreak occurred in the north of Germany in 1995 in which over 100 horses died. Since the turn of this century increasing numbers of cases have been reported all across northern Europe, including in the UK, but most particularly north Germany, Belgium and France.

This was an emerging, new, often fatal, disease and nobody had any idea what was causing it.

The hunt for the cause

Often the first step taken in the face of an emerging new disease is for epidemiological data to be accumulated, to see if any distinct patterns emerge. A team at the University of Liège in Belgium, associated with research worker Dominique Votion, established an informal liaison group with the acronym AMAG, the Atypical Myopathy Alert Group, that began to collate information from clinicians dealing with cases. Any reported case triggered completion of a detailed questionnaire about the type of horse involved, the type of premises, the events preceding the outbreak, and the nature of the husbandry in place. Since its inception over a thousand cases of the disease have been reported in detail through AMAG, and it was through this international collaboration that initial hints at causation began to immerge.

Why Atypical?

As long as people have written about horses there have been reports of myopathy associated with exercise. What we now refer to as Exertional Rhabdomyolysis (ERM – rupture of muscle cells as a result of exercise) has been a familiar part of living with the horse for centuries. Its nicknames over the years included 'set fast', 'tying up' or 'Monday morning disease'.

As the latter name suggests, this disease was most often seen in working horses after they'd had Sunday off, and resumed their labours on Monday morning. It was a disease characterised by muscle stiffness, sweating, raised heart rate and, in severe cases, rupture of muscle cells leading to the passage of myoglobin in the urine. It's a disease of well- or over-fed horses, often seen following a short reduction in work. The big difference with Atypical Myopathy is that almost all of the epidemalogical features of the disease are exactly the opposite of those encountered in ERM. The classic case of Atypical Myopathy occurs in a horse which is permanently at relatively poor overgrazed pasture, in normal or light bodily condition, has very little additional feed, and almost invariably has had no exercise. These horses are simply found profoundly ill, often unable to move, unable even to keep their heads up, and in many cases collapsed, or worse still dead.

Common factors

As the death rate mounted, the race was on to try to find the cause. Once the data collation centre at Liège was established, it quickly became apparent that the outbreaks followed very similar patterns, irrespective of the country concerned. The most striking feature was seasonality.

Almost all the cases occurred in autumn, with a few occurring the following spring, particularly in years where many cases had occurred the preceding autumn. There were other common factors, the most obvious of which was an association of the paddock with trees. While it wasn't certain what this association was, over and over again outbreaks were associated with pasture in which there were fallen leaves, rotten dead branches, or simply the presence of trees themselves. Pastures sited on a sloping gradient were also over-represented, and it wasn't clear initially why on earth this should be the case.

Weather conditions too played a part. In the week preceding an outbreak, vets commonly reported that there had been cold, wet, windy weather. Conversely, in the middle of an outbreak, a period of three or four days of frost or snowfall seemed to stop it in its tracks.

Although the disease struck all age groups, horses below the age of three were by far the most often affected.

People looked at moulds and fungi initially, because these are well known to occur in cold and wet weather in the autumn, and also to be able to produce powerful mycotoxins, but no obvious culprit came to light.

One of the big problems with the investigation of this disease was the relative paucity of funding. Most of the grant-awarding bodies have specialist interests, and this was a disease of the pastured leisure horse or pony, not of valuable thoroughbreds. Funds were therefore hard to come by, and this led researchers to doing the work that was time-consuming but cheap, i.e. compiling data of the epidemiology of the outbreaks, rather than intense toxicological research that needed to be funded. With most cases dead, owners were certainly not going to be the source of this research funding.

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Figure 2 The chocolate brown/port wine coloured urine almost always seen in cases of Atypical Myopathy, and a chilling clinical sign to see given the prognosis

Clinical signs

All of the recorded outbreaks listed the same clinical features. These included weakness, stiffness, inability to move, apparent difficulty in breathing, raised heart rate, congested mucus membranes and often collapse. Urine passed was dark chocolate brown in almost all cases. The majority of cases, if not found dead, would die within 72 hours. Despite being dull, the appetite was often not affected.

Histopathology

Because so many of these cases died, there was an abundant source of post-mortem material for researchers to examine. The first thing they noticed was that the predominant attack was on the type 1 muscle fibres. These are often known as 'slow twitch' and are involved in things like posture and respiration, rather than the type 2 muscle fibres ('fast twitch') involved in galloping.

The affected muscle fibres showed a characteristic histopathology, called Zenker's degeneration, which reflects starvation of energy. This was accompanied by accumulation of lipids in and around the cells, so it looked as if the disease was produced by something that prevented muscle cells from metabolising fat.

This type of muscle degeneration had been seen before in people. In humans there is a condition called 'Jamaican Vomiting Sickness' which is triggered by ingestion of Ackee fruit. This fruit contains a toxin, Hypoglycin A. Hypoglycin A acts on muscle cells in a characteristic way, preventing them from metabolising fat effectively. The syndrome in man is known by the acronym MADD, (Multiple Acyl Coenzyme A Dehydrogenase Deficiency).

Mitochondria are the energy production units within each cell, the 'power station', and in type 1 muscle fibres produce energy primarily by breaking down fat using the enzyme Acyl CoA. If this enzyme is deficient, either because of an inherited genetic disorder or because of the effects of toxins, then the mitochondria within the cell simply cannot produce energy, the cell starves to death and dies. So was it possible that Atypical Myopathy was being produced by a toxin preventing these mitochondria from working, as in the human disease?

Clinical pathology

If this was the case then we would expect to find changes in the blood reflective of this, and we did. Serum samples taken from affected cases showed massive rises in muscle enzymes Creatin Kinase and Amino Aspartate Transferase. These are the same muscle enzymes we look for in 'tying up', but the levels in the atypical cases were massively elevated, often in the hundreds of thousands or millions of international units/ml of blood. A lot of muscle cells were dying. In addition to this, there were rises in lactic acid and isomers of Acyl Carnitine, which seemed to indicate that just such events were taking place in the muscle cells; they were being prevented from metabolising fat.

The breakthrough

Epidemiological data accumulating over the years, combined with histopathological studies on the

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ROB PILSWORTH

Figure 3 *A splendid example of the Sycamore (Acer pseudoplatanus) (3a) 'hooching' with samaras ready to drop. This tree is in the border of a stud paddock in the Newmarket area. The ground below (3b) is covered in fallen samaras*

damaged muscle cells, and biochemical studies on serum, had all pointed tantalisingly to a likely common cause in some sort of toxin. The European scientist Van Galen had suggested that trees must play a significant role, in that they were found on 98% of the European pastures on which myopathy typically occurred. Even then people were looking for a fungus or a side product of the presence of trees, rather than the tree itself. The breakthrough finally came in 2006 when a muscle research group based at the University of Minnesota linked to the eminent muscle researcher Stephanie Valberg published a case series of cases spanning 1998 to 2005. The disease, which they called Seasonal Pasture Myopathy, presented in exactly the same way as the European cases, and had exactly the same biochemical profile of the MADD syndrome.

But the breakthrough fact was that the Box Elder (Acer Negundo) was present in every single case, and not on unaffected premises. They knew that the toxin Hypoglycin A could cause the symptoms of MADD and therefore Atypical Myopathy. So could the Box Elder trees be responsible?

Analysis of the seeds of these trees provided the missing link. They contained variable to high levels of Hypoglycin A. Valberg and her colleagues had had the good fortune not only to correlate the epidemiological data on their outbreaks, but also to receive funding from the Minnesota Rapid Agriculture Response Fund, which allowed them to look in detail for possible toxins.

Once the toxin had been confirmed in the American cases, attention then turned to the huge library of stored samples from European cases at the University of Liège. This confirmed Hypoglycin A and its metabolites were found in the serum and urine of all the affected European horses too. As the Box Elder was not present in most of Europe, another tree had to be the culprit. Another species of Acer, Acer Pseudoplatanus (the Sycamore tree) had been present on almost every premises logged in the European outbreaks. Analysis of the familiar 'helicopter seeds' of the Sycamore tree (known correctly as samaras) proved positive – they contained Hypoglycin A.

The pieces fall into place

Suddenly, all the epidemiological data made sense. The link with trees, fallen branches and leaves was clear; this merely indicated the presence of trees either around or in the paddocks. Similarly, cold, wet, windy weather results in massive falls of the seeds from the trees, allowing their ingestion. Other factors suddenly started to make sense. The disease was linked with pastures that are relatively poor or over-grazed, and on which no supplementary feeding takes place. Hungry horses will eat unsuitable material. Similarly the link with youngsters had a possible basis – young horses will nibble at all sorts of unsuitable forage, whereas mature horses become more 'picky'.

The link with hillside paddocks nods to the topography. Hilly regions get increased winds, and winds blow down and spread the samaras. Because of these winds, the paddocks are likely to

incorporate easily grown tree shelter-belts, often including Sycamore.

One outstanding difficulty of the samara toxin theory was the occasional outbreaks which occurred in spring. What was causing these? The multi-disciplinary research group based at the University of Liège solved this riddle in 2016 by showing that the seedlings of the Sycamore tree are also potential sources of Hypoglycin A. The source of the spring outbreaks had been identified.

What to do in the face of an outbreak

Remove all co-grazing horses from the affected paddock and stable them, or put into a paddock not contaminated with the samaras or seedlings.

Test the unaffected horses for raised muscle enzymes, a quick and easy test that most equine practices can do, and, if found, consider intensive fluid therapy, nutritional support and vitamin treatment in an equine hospital. This has been shown to increase the chances of survival.

Consider testing all co-grazers for Hypoglycin A and its metabolites. The problem with this is it is relatively expensive (approximately £100 per horse), can be done only at specialist labs (so delays), and is not totally predictive of the development of the disease, or even eventual survival.

Subsequent events

Since the milestone paper published by the Valberg group and conformation that the toxin responsible for the American Seasonal Pastural Myopathy, and European Atypical Myopathy were the same toxin Hypoglycin A, various other parts of the jigsaw have fallen into place. An assay for Hypoglycin A and its metabolites has been developed so that horses, and the seeds of the trees, can be specifically tested for this poison. In the UK, this test is offered by Richard Piercy's group at the Royal Veterinary College, London (https://www.rvc.ac.uk/research/laboratories/comparative-neuromuscular-diseases-laboratory/diagnostic-services).

Intriguingly, it's now been found using this test that horses grazing pastures covered in the samaras of the Sycamore tree will often have raised blood levels of Hypoglycin A, without developing the disease.

Other research showed that the samaras can be blown up to 200 metres from trees, which probably explains the occasional incidence of Atypical Myopathy where no Sycamore trees are recorded in the paddock.

In 2016, the disease was reported from New Zealand, where four horses had been affected two years earlier. Two of the horses sadly died, but in all cases the toxin Hypoglycin A was detected in the serum of the horses and not detected in the serum of healthy control horses. The samaras from both the Sycamore Maple and the Box Elder were detected on the paddocks and samples tested from throughout New Zealand also showed the presence of the toxin in the majority of cases.

Questions

It is very satisfying that the multi-disciplinary approach to this disease, cataloguing the epidemiological factors, the pathology, the changes seen in the muscle under the microscope, and comparative medicine studies looking at similar diseases in man, have led to the cause being found. However, many questions remain:

Why is it that only some horses on affected pastures go down with the disease where others with blood levels of Hypoglycin A present do not?

Why is it that the disease appears to be of relatively recent emergence in large numbers when the Sycamore tree has been abundant in the countryside since the middle ages?

Why is it that in some years many cases are recorded and in others few?

The main suspect for the emergence of the disease is climate change. The north European climate is undoubtedly undergoing flux at the present time and this may have repercussive effects on both the level of toxin in the seeds, and the increase in late autumn storms which produce their mass deposition on the pasture. Although many cases have been recorded on non-thoroughbred breeding farms, to date there have been only a few cases on thoroughbred studs, although those recorded have ended with fatalities.

This is almost certainly due to the fact that supplementary feeding, and careful management of pastures to avoid over-grazing, means these horses often just don't eat the samaras. They have other more attractive food to eat. Since the demonstration of the link to the Sycamore, many stud farms have used the therapeutic chain-saw to remedy the situation. However, on a recent walk on a public footpath running through the middle of a Newmarket stud farm, I counted over 20 Sycamore trees showering their samaras into the adjacent paddocks, so the challenge is certainly still present.

The reason Yew trees mainly grow in churchyards is that, because of their threat to livestock, through the poison, taxene, present in their berries, they were not tolerated on grazing land. To date, it seems our management methods in relation to feeding and grazing practices have allowed the thoroughbred industry to get lucky, but that could change and this may be a good time for studs to re-evaluate their approach to this potentially really awful disease.

PREVENTION

Prevention is always better than cure, especially in a disease where the majority of cases die, so perhaps consider the following:

Where possible, take out Sycamore trees from and around equine paddocks. If not possible, consider fencing off the 'drop zones' for the samaras and resultant seedlings.

Screen paddocks in the autumn for the presence of the 'helicopter seed' samaras (see fig 3b). If abundant, take action to clear them, or limit grazing access.

Prevent horses grazing where abundant seedlings are growing in the spring.

Keep aware of alerts for increased Atypical Myopathy years via the website alerts from AMAG (http://labos.ulg.ac.be/myopathie-atypique/en).

Avoid overgrazing of paddocks.

Give supplementary food and forage during the risk periods, so the horses are not tempted to eat the samaras.

Regular de-worming programme, guided by the faecal egg count.

Consider not using any disease-associated paddock for grazing in autumn and spring.