Atypical myopathy is an acute intoxication induced by the ingestion of hypoglycin A, a toxin contained in the seeds and seedlings of certain trees of the genus Acer (particularly Acer pseudoplatanus [sycamore] in Europe), which results in disruption of the energy metabolism. The clinical signs arise from energy depletion in the type I fibres of the postural and respiratory muscles, and lead to a specific biochemical profile that may be used to confirm a diagnosis. Since there is no cure for the condition, the emphasis is on prevention, which requires knowledge of the conditions necessary for the causative agent to exert its toxicity. This article gives an overview of atypical myopathy, discussing the mechanism involved, its aetiology and the clinical signs and management (therapeutic and prevention).

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History of atypical myopathy in Europe

From sporadic cases to large outbreaks

In 1984, an apparently new equine myopathic syndrome named atypical myoglobinuria was reported (Linklater 1984). Horses kept at grass were suddenly presenting with an acute myopathic syndrome that was not induced by exertion; most of the affected animals died within a couple of days. Since then, outbreaks of this condition (which was later renamed atypical myopathy) have occurred sporadically in the autumn but, over the past decade, large series of cases have been observed repeatedly in several European countries not only in the autumn (Fig 1) but also in the spring (van Galen and others 2012a). Since autumn 2000, more than 1800 cases of atypical myopathy have been recorded throughout Europe by the Atypical Myopathy Alert Group (AMAG), an informal group set up in 2004 comprising veterinarians and researchers (Table 1).

Cases are reported on a spontaneous basis and result mainly from observations via social media and a dedicated website: www.myopathie-atypique.be. As the performance of this type of investigation does not exceed 5 per cent (Dufour 1994), it can be roughly estimated that the number of equids affected since autumn 2006 is tens of thousands.

Discovering the cause

By gathering information on cases of atypical myopathy throughout Europe via the dedicated website, knowledge about its epidemiology has grown year by year. The centralisation of cases allowed information to be obtained in real time (ie, when cases occurred), which enabled relevant samples to be collected to help determine the pathophysiological mechanism. Samples obtained at postmortem examinations showed that the myodegenerative process of atypical myopathy is selective and affects postural and respiratory muscles rather than locomotor muscles (Gassart and others 2007); histology revealed that the acute myonecrosis process (Fig 2) affects the type I fibres (ie, oxidative fibres) that are involved in lipid storage. Analyses of blood and urine samples revealed a multiple acyl-coenzyme A (CoA) dehydrogenase deficiency (MADD) that prevents affected horses using the most efficient energy source – lipids – resulting in them having to rely solely on carbohydrate metabolism (Westermann and others 2008). Identification of this metabolic defect was a key step in the discovery process since it guided the search for the aetiological agent towards toxins that cause this biochemical defect.

In addition, detailed knowledge of the epidemiology of atypical myopathy suggested that the aetiological agent had an environmental origin (Votion and others 2007, van Galen and others 2012a) and it was hypothesised that, on overgrazed pastures, horses might ingest grass contaminated with soil containing a toxin and/or eat plants that should normally not be consumed by equids. However,
at that time, no specific plants had been implicated in the aetiology of atypical myopathy. *Ranunculus repens* and *Acer pseudoplatanus* (the familiar sycamore tree in northern Europe, Fig 3) were the only plants both present on premises surveyed in Belgium (Votion and others 2007). The contribution of trees (in general) to the pathogenesis of the disease was eventually suggested by van Galen and others (2012a), who found trees were present on 98 per cent of European pastures on which cases of atypical myopathy occurred. Van der Kolk and others (2010) suggested that *A pseudoplatanus* leaves contaminated with an endophyte (Fig 4) had a role in the aetiology of the condition but scientific evidence for this is lacking. *Clostridium sordellii* has also been suspected of being involved (Unger-Torroledo and others 2010) but, again, evidence is lacking.

In 2006, a similar condition called seasonal pasture myopathy was recognised in the USA (Finno and others 2006); cases also exhibited a MADD-like biochemical profile (Sponseller and others 2012). Following a botanical survey, it was hypothesised that the condition was caused by ingestion of seeds from *Acer negundo* (box elder tree) (Fig 5) as these trees were present on all pastures associated with cases. Hypoglycin A – a toxin known to cause acquired MADD in people (Tanaka and others 1972) and found in the seeds of some *Acer* species (Fowden and Pratt 1973) – was found in *A negundo* seeds collected on the pastures and its metabolite, methylenecyclopropyl acetic acid (MCPA), was found in a conjugated form in the serum (ie, MCPA-carnitine) and urine (ie, MCPA-glycine) of affected animals (Valberg and others 2013).

By analysing blood samples collected over the years in Europe, it was concluded that atypical myopathy, like seasonal pasture myopathy in the USA, is highly associated with MCPA-carnitine, the toxic metabolite of hypoglycin A (Votion and others 2014). However, in Europe, the source of hypoglycin A appears to be the seeds of *A pseudoplatanus* (Unger and others 2014) in the autumn, and its seedlings in the spring (Baise and others 2015).

**Is atypical myopathy equine specific?**

Although it is considered to be a species-specific disorder, other pasturing animal species might suffer from atypical myopathy. In the 1970s, an outbreak of acute myopathy of unknown origin occurred in a group of cattle kept outside in the winter (Linklater 1977). For various reasons (eg, monogastric versus polygastric digestive systems), horses may be more susceptible than other species to the phytotoxin causing the condition. Epidemiological and clinical data gathered from European outbreaks suggest that donkeys and zebras may also suffer from the condition (van Galen and others 2012a).

**Toxic mechanism**

Once ingested, hypoglycin A is metabolised into MCPA, a toxic compound that disrupts the energy metabolism.
This then combines with CoA to form MCPA-CoA, which inhibits acyl-CoA dehydrogenases that are involved in the metabolism of short- and medium-chain fatty acids. MCPA-CoA also inhibits acylcarnitine-CoA transferases that are involved in the transport of long-chain fatty acids into the mitochondria, where they undergo beta-oxidation, and interferes with the amino acid metabolism (but to a lesser extent). These biochemical disorders result in the accumulation of acylcarnitines in the blood, which leads to the acquired MADD biochemical profile observed in affected animals. MCPA-carnitine is present in blood and is eliminated in urine as MCPA-glycine.

The clinical signs of atypical myopathy and seasonal pasture myopathy therefore result from energy starvation in muscle fibres whose predominant energetic pathways rely on oxidative metabolism. In resting animals, these are mainly the muscles involved in posture and breathing, and the heart muscle.

Clinical presentation and diagnosis

Affected animals initially exhibit muscle weakness and stiffness, and an inability to stand, which rapidly progresses to recumbency. They are frequently dyspnoeic, which often leads to death (74 per cent mortality rate [van Galen and others 2012a]). Cardiac signs are generally mild (slightly raised heart rate, heart murmurs).

All the clinical signs result from the massive destruction of the targeted muscle groups. However, the incidence of specific signs may vary from one year to another. For example, in autumn 2013, heart murmurs were more frequent and there was less recumbency in affected animals compared with previous years (Table 2).

A clinical diagnosis of atypical myopathy can be made based on the history, clinical signs, laboratory findings and histology of muscle specimens, as summarised in Table 3.

Management

Therapeutic measures

Atypical myopathy is often fatal and, to date, there is no specific cure. Nevertheless, a comparative study of survivors versus non-survivors demonstrated that treatment significantly increases the animal’s chances of survival (van Galen and others 2012b). The main aims of therapy are to:

- Limit further muscle damage;
- Restore the circulating volume;
- Correct acid–base and electrolyte disturbances;
- Provide energetic substrates that are usable by muscle cells;
- Provide vitamins and antioxidants; and
- Alleviate pain, if present.

These measures are largely supportive and symptomatic, but it is worth noting that the only therapeutic groups that appear to be beneficial are vitamins, antioxidants (vitamins B, C and E, and selenium) and carnitine (van Galen and others 2012b); in particular, supplementation with riboflavin (vitamin B2) might improve the compromised mitochondrial function. Since atypical myopathy severely affects the energy metabolism by blocking several steps in the aerobic mitochondrial lipid metabolism (Westermann and others 2008), nutritional support is important. Glucose infusion is recommended as well as a diet poor in lipids and rich in carbohydrates, which should be regularly offered to affected animals (except those that have dysphagia with or without oesophageal obstruction) to provide energy. As the toxic metabolite is secreted in urine, a large amount of perfusion is advised.

These general recommendations have been extensively described by van Galen and Votion (2013a, b).

Prevention

Discovery of the cause of atypical myopathy has had major implications for prevention of the condition. As well as following previous recommendations that have been widely described elsewhere (Votion 2012), it is advisable to:
Screen the pasture in early autumn to check for the presence of samaras (seeds) and, if found, the horses should be removed from the field;

- Prevent horses ingesting the toxic seedlings in the spring;
- Try to remove the aetiological agent (i.e., collect the seeds and burn them), although this may not be possible if they are too abundant (Fig 6);
- Follow alert messages via the atypical myopathy website (Votion 2004) and manage horses accordingly;
- Manage pasturing time according to weather conditions.

Outbreaks of atypical myopathy are triggered by inclement climatic conditions, possibly by making the causal agent easily accessible for ingestion when wind or heavy rain brings vegetation to the ground.

The author is currently undertaking field studies to establish a system of risk-based prevention (probable emergence of cases based on monitoring the toxicity of seeds, which may vary during the season) rather than a system based on the observation of cases (current alert system) (Box 1).

Aetiological agent

Emerging disease

It is not known why atypical myopathy has suddenly appeared in Europe when the tree thought to be involved with the aetiology – the sycamore – has been naturalised for many decades. To prevent atypical myopathy, it is necessary to understand how the pathogenic system develops. One reason for the emergence of cases may be the observed climate changes of recent years that might increase the production of samaras (Vitasse and others 2009) and/or impair their maturation-dormancy stages (in association with a variation in the degree of toxicity).

In addition, it might be hypothesised that unripe seeds contain a higher level of the toxic hypoglycin A than ripe seeds. Epidemiological investigations have highlighted the contribution of environmental factors as factors that trigger outbreaks. In particular, wind seems to predispose the onset of clinical signs. The greater severity of storms and/or the occurrence of storms earlier in the year than previously might also contribute, resulting in samaras being removed from trees at a stage of maturity when they are more toxic. However, one must keep in mind that the development of atypical myopathy is probably multifactorial.

Other possible explanations for the emergence of the disease are that an increased number of pastures border forests, that there is a greater density of A. pseudoplatanus and/or geographical extension over time and, finally, possibly an increased susceptibility of horses following changes in their management and/or use over recent decades.

Table 2: Main clinical signs of atypical myopathy in autumnal outbreaks in Europe

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Number of cases</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Autumn 2006 to 2009 (percentage) (n = 356, N = 600)*</td>
</tr>
<tr>
<td>Pigmenturia</td>
<td>93</td>
</tr>
<tr>
<td>Weakness</td>
<td>85</td>
</tr>
<tr>
<td>Stiffness</td>
<td>83</td>
</tr>
<tr>
<td>Depression</td>
<td>80</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>79</td>
</tr>
<tr>
<td>Recumbency</td>
<td>78</td>
</tr>
<tr>
<td>Trembling</td>
<td>68</td>
</tr>
<tr>
<td>Sweating</td>
<td>64</td>
</tr>
<tr>
<td>Normothermia</td>
<td>60</td>
</tr>
<tr>
<td>Distended bladder on rectal palpation</td>
<td>58</td>
</tr>
<tr>
<td>Congested mucous membranes</td>
<td>53</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>44</td>
</tr>
<tr>
<td>Colic</td>
<td>27</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>25</td>
</tr>
<tr>
<td>Heart murmurs</td>
<td>21</td>
</tr>
</tbody>
</table>

*van Galen and others (2012a)
†Unpublished preliminary data
N Total number of cases reported to the Atypical Myopathy Alert Group
n Number of cases with confirmed, or a high probability of, atypical myopathy
n* Number of files considered (very preliminary data)
### Is A pseudoplatanus the only toxic maple tree in Europe?

For all cases of atypical myopathy recorded in autumn 2013 and spring 2014, seeds or seedings of A pseudoplatanus were found in the direct vicinity of the horses affected (unpublished data). However, information from cases in autumn 2013 indicate that the absence of A pseudoplatanus in or around fields is not a sufficient guarantee to guard from atypical myopathy: samaras were found on pastures where there were affected animals even though the closest tree was over 200 meters away.

A negundo is not indigenous to Europe but tends to establish itself and was observed in the pasture of one Belgian case (Votin and others 2014). Other Acer species that have also been found on some pastures associated with atypical myopathy cases are Acer platanoides (Norway maple) and Acer campestre (field maple). These two trees are considered to be ‘non-toxic’ (Fowden and Pratt 1973, Westermann and others 2016).

The toxicity of seeds of many Acer species was determined in a study conducted 40 years ago (Fowden and Pratt 1973), but it did not take into account possible seasonal and annual variations in toxicity. Therefore, although the toxicity of A pseudoplatanus and A negundo has been confirmed (Fowden and Pratt 1973, Valberg and others 2013, Unber and others 2014), the innocuousness of other Acer species across Europe needs to be checked by hypoglycin A quantification using validated methodology.

### Are maple trees the only cause of atypical myopathy in Europe?

Acer species belong to the Sapindaceae family. This contains almost 2000 species of trees and includes Aesculus hippocastanum (horse chestnut tree), which is very common in Europe. To the author’s knowledge, no research has been conducted to determine the presence of the toxin in the seeds of European tree species other than maples.

Fraxinus excelsior (European/common ash), belonging to the Oleaceae family, was frequently found on the pastures of affected horses (Patarin and others 2011). The seeds of several members of this family contain pharmacologically active substances but hypoglycin A has not been specifically searched for in the fruits of these plants. Moreover, there are no data available on the toxicity of the leaves of plants in the Sapindaceae or Oleaceae families. Other trees and shrubs that produce samaras, such as Corylus avellana (common hazel, Betulaceae family), Fagus sylvatica (European/common beech, Fagaceae family) and Populus species (Salicaceae family), were also frequently present in or around the pastures associated with cases in autumn 2013 (unpublished data). Further research is needed to check the toxicity of other trees that are in close proximity to pastures where cases of atypical myopathy occur.

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