Focus Article: Update in the cause of Atypical myopathy
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Introduction
Atypical myopathy (AM) was first recognized in grazing horses in 1934 in East Scotland and first reported in the literature in 1985. The condition was named as Acute Myopathy or Atypical myoglobinuria due to clinical signs noticed in the first identified cases. Early reports described recumbent and weak horses that often died within the first 12-72h. Suspected cases sporadically occurred in several countries such as the USA, Canada and Australia, although it was named as seasonal pasture disease in these locations. The first major outbreak, which raised awareness of the condition worldwide, occurred in Germany in 1995. Since 2000, numbers of outbreaks and affected animals increased considerably in central Europe, triggering the beginning of epidemiological investigations into the mechanisms of disease and methods for its prevention.

Surveillance in Europe
As a leading group, The University of Liege (Belgium) established an informal epidemiosurveillance network known as the Atypical Myopathy Alert Group (AMAG) that in 2006 expanded their national recording of cases to all European cases. Currently, this network consists of worldwide equine veterinarians, national epidemiological networks, and other collaborators such as universities. AMAG’s aim is to exchange information about the occurrence of outbreaks of this disease and to initiate collaborative research.

Number of cases reported to AMAG from 2006 to 2013
A real breakthrough identifying the cause

Factors linked to environmental toxins were considered as potential causative agents for AM from the beginning. Consistent findings in pastures where AM cases were reported contained dead leaves and wood, they were usually surrounded by trees and had frequently contained wet areas. However, epidemiological studies and particularly the histopathological examination of muscle sections from affected animals have furthered the understanding of the AM pathophysiology guiding investigations towards mitochondrial disorders of toxic origin. Several environmental toxins, including Clostridium sordellii toxins or Rystisma acerinum mycotoxins, which lead to dysfunction of mitochondrial metabolism, were subsequently investigated with inconsistent results.

Subsequent research was informed by similar conditions in human medicine that may share common clinical signs and histopathological features with AM. Morphopathological examination of AM cases showed an acute and degenerative process as a result of intracellular accumulation of lipids in the slow oxidative type I-muscle fibers, which are more prevalent in postural and respiratory muscles.

![Figure 1](image1.jpg)

**Figure 1:** Simplified mechanism of β-oxidation during in the muscle cell. The picture shows the importance of carnitine and different acyl-coA enzymes in the transport of fatty-acids into the mitochondria and their contribution to lipid metabolism.
These observations along with the biochemical changes present in AM cases suggested an impairment of fatty acid oxidative metabolism, especially the β-oxidation, therefore sharing multiple similarities with acyl-CoA dehydrogenase deficiencies (MADD) in man, and particularly an acquired MADD condition called Jamaican vomiting sickness. This disease is triggered by the ingestion of ackee fruit that contains hypoglicyn A that is metabolised into the mitochondria of the muscle cell to methylenecyclopropyl acetic acid (MCPA). This metabolite decreases the production of nicotinamide adenine dinucleotide (NADH) and acetyl CoA. Studies conducted in the USA and then in Europe found increased levels of MCPA in AM affected horses.

In human studies, once hypoglycin A is activated in the mitochondria, it irreversibly inhibits medium and short acyl-CoA dehydrogenases, which are essential for β-oxidation of fatty acids and boosting the accumulation of fatty acids and other metabolites and key enzymes of mitochondrial energy metabolism. Furthermore, MCPA may also bind acyl-CoA and carnitine, disrupting the carnitine-acyl-CoA transferase system by impairing the transport of long-chain fatty acids into the mitochondrion. As a result of this inhibition, fatty acids are not only accumulated in the mitochondria but also in the cell cytosol leading to the intracellular accumulation of fatty acids characteristic of AM.

![Figure 2. Proposed mechanism of action of MCPA: accumulation of fatty acids (showed in yellow) within the mitochondrion followed by excessive lipid storage in the myocyte (showed in yellow). The impairment of the lipid metabolism leads to myocyte degeneration and Zenker necrosis of the muscle.](image)

Type I myofibrils depend largely on fatty acids as their primary energy source, and are the predominant fibre type in postural, cardiac and respiratory muscles explaining the profound muscular weakness and respiratory dyspnoea seen in AM horses. As lipid metabolism is blocked and oxygen delivery impaired by failing cardiac and respiratory muscles, metabolism becomes more reliant on anaerobic glycolysis resulting in muscle glycogen depletion and lactic acidosis.

Although great similarity exists between AM cases and human MADD cases some differences should be acknowledged. Horses with AM show hyperglycemia and increased free serum carnitine levels, whereas humans with MADD have hypoglycemia and decreased free carnitine levels. These differences may be explained by species-specific steps in energy metabolism although further research in horses is required to confirm this. It is believed that the hyperglycemia in horses might reflect higher hepatic glucose obilization from liver glycogen stores and possibly insulin resistance.
Finding hypoglycin A

The presence of trees in or around the pastures where AM cases are reported is a common feature in Europe and the USA, although the species found vary considerably between countries and even between outbreaks in the same country. Several trees from the family Sapindaceae produce fruit or seeds containing hypoglycin A, although it might be other families involved. *Acer negundo* (box elder) has been linked recently to cases of atypical myopathy in the USA and its seeds found to contain different concentrations of this substance. This particular tree is not usually present in Europe and it has not been encountered in pastures where AM were reported. However *Acer Pseudoplatanus* (sycamore maple) was consistently found on AM pastures in some European studies and mentioned in botanical surveys of European pastures. Other *Acer* species such as *Acer platanoides* (Norway maple) and *Acer campestre* (field maple) have also been found on some pastures but their seeds do not seem to contain hypoglycin A. The level of hypoglycin A in the seeds is variable and can be affected by a number of environmental factors. For example, dry conditions, compacted soil, wind strength among others may affect the seed load, seed dispersal and concentration of different substances in fruits and seeds. In other plant species, abiotic stress can significantly increase biochemical defenses and increase the concentration of certain aminoacids.

Unfortunately, accurate botanical surveys are not widely available in the areas where AM cases have been reported and detection of Hypoglycin A in seeds encountered in these pastures has not been performed to date in Europe. Thus this opens a new route of investigation for AM evaluating correlations between the presence of disease and plant species and the interactions between horses and maple species.

Therefore the general recommendation for owners should be to keep the horses away from pastures surrounded by these trees during the risk season or reduced the amount of seeds in the pastures. Feed supplementation in sparse pastures might also help to avoid foraging during the risk season.

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*We encourage reporting AM cases through: www.myopathieatypique.fr/espace-professionels/veterinary-form/*

*List of references is available on author request*