University of Veterinary Medicine Budapest

Department of Botany

Equine Atypical Myopathy as a result of Sycamore toxicosis

Evgeniya Boytsova

Supervisor: Dr. Cserhalmi Dániel, Associate Professor

Department of Botany

Table of Contents

List of abbreviations

AM – Atypical Myopathy

AST – Asparate Aminotransferase

BPM – Beats Per Minute

CK – Creatine Kinase

ER – Exertional Rhabdomyolysis

GYS1 – Glycogen Synthase 1

HGA – Hypoglycin-A

IU/L - International Units Per Liter

LD_{50} – Lethal Dose 50 percent

MADD - Multiple Acyl-CoA Dehydrogenase Deficiency

MCPA - Methylene Cyclopropyl AceticAcid

NSAIDs – Non-Steroidal Anti-Inflammatories

ORO - Oil Red O

PSSM – Polysaccharide Storage Myopathy

RER – Recurrent Exertional Rhabdomyolysis

SPM – Seasonal Pasture Myopathy

1. Introduction

The thesis will be focused on covering the pathophysiology following consumption of the seeds of the sycamore maple tree *(Acer pseudoplatanus)* in horses. Consumption of these seeds may lead to development of atypical myopathy (AM), which is a muscular disease that has been reported in approximately 20 different countries within the European continent [1]. The thesis will also try to inform owners on how to prevent toxicosis and discuss why it is more prevalent in certain areas, the seasonality of intoxication, and how to recognize and differentiate AM from other myopathies. Ultimately, I will try to determine the most effective diagnostic methods and treatments for addressing AM.

Atypical myopathy bears a close resemblance to seasonal pasture myopathy (SPM), which occurs in the North American continent particularly in the United States and Canada. AM or SMP occurs consequently following ingestion of seeds or seedlings, this is due to the amino acid known as Hypoglycin-A (HGA) being converted into a toxin in the horse, although it is important to note that currently it is not confirmed for a fact that HGA is responsible [2]. The sycamore tree is part of the *Acer* genus, and currently there are 25 different known species of the genus. Extensive studies suggest that it is primarily *Acer pseudoplatanus* that contains HGA and consequently results in equine AM. It is also worth mentioned that HGA has also been found in the box elder tree (*Acer negundo*), which is the primary contributor of SPM in North America [1].

AM is a highly significant and important disease in Europe due to its frequent and fatal nature. It is a seasonal pasture myopathy that emerges suddenly and unexpectedly. The disease has been extensively studied, and various epidemiological investigations have been conducted to understand its aetiology and develop preventive measures, however efficient and effective therapeutic measure have not been described and as such the following thesis will attempt to do so. AM outbreaks have been reported in several European countries, including Belgium, Germany, France, Denmark, United Kingdom, Spain, Switzerland, and the Netherlands [3]. The number of reported cases has been increasing, and large outbreaks occur at regular intervals in some countries. Belgium, Germany, and France have experienced the most significant outbreaks [2]. The disease is characterized by acute illness and a high fatality rate therefore practitioners need to be well-prepared to handle critically ill AM patients. Overall, the

importance of atypical myopathy in Europe stems from its high fatality rate, the frequency of outbreaks, and the need for preventive measures. Understanding the disease's etiology and developing effective diagnostic procedures are crucial for managing and preventing future cases.

2. Objectives

This work aims to

a) raise awareness regarding sycamore toxicosis in companion horses to owners, the equine community and veterinarians, especially in regions prone to intoxications and how these intoxications occur.
b) review pathogenesis and observed differences in clinical symptoms, what can cause similar manifestation of symptoms similar to atypical myopathy and how to differentiate them.
c) review diagnostic methods used and what treatment methods were implemented to determine if there are courses that prove to be more effective than others.

3. Atypical myopathy in general

3.1 Epidemiology

Atypical myopathy was first discovered in the Wallon region of Belgium in 2004, with the first exploratory data analysis being published by Votion et al. in 2008 [11]. Atypical myopathy is an acute form of rhabdomyolysis that can affect grazing horses in both epizootic and sporadic forms. It is believed that the ingestion of HGA, a poisonous compound present in the leaves of specific trees, is the likely cause. Epidemiological studies have revealed several risk factors associated with the disease, including the size of the pasture, the number of animals with access to the pasture, and the management practices employed. Vaccination and regular deworming have been found to be protective against the disease, while using the horse for work has been associated with an increased risk. Overall, it appears that the risk of atypical myopathy can be minimized by employing careful management practices and avoiding areas where HGA is found [4].

As mentioned previously, AM has been encountered in Austria, Belgium, England, France, Germany, Italy, Luxembourg, Scotland, The Netherlands and Switzerland and multiple other European counties [5]. Also noted as similar to most diseases, that horses under the age of 5 years old and horses over 20 years old are more susceptible to the disease [6]. Another study revealed that foals under the age of 4 months were not affected by AM, and that certain pastures might be particularly at risk of contracting AM due to their moist, sparse environments [4].

3.2 Comparison between seasonal pasture myopathy and atypical myopathy

A comparison of seasonal pasture myopathy and atypical myopathy reveals some similarities in clinical signs and biochemical profiles, suggesting that both myopathies may have a similar pathogenesis. SPM was first observed and seen in horses located in midwestern United States. SPM manifests as an acquired multiple acyl-CoA dehydrogenase deficiency (MADD) and is linked to the consumption of the HGA, which is present in the seeds of box elder trees in affected pastures. In contrast, atypical myopathy is a myopathy that is reported with increasing frequency in Europe. It is characterized by an acute onset of severe muscle weakness and is associated with the ingestion of the European sycamore maple tree. Both myopathies share some key clinical features, including muscle weakness and a high serum creatine kinase (CK) activity. Furthermore, serum from horses affected by both conditions contains the conjugated toxic metabolite of HGA, known as methylenecyclopropyl acetic acid (MCPA). Additionally,

both conditions are linked to morphological changes in oxidative muscles and alterations in mitochondrial structure. In summary, it is probable that MCPA-carnitine, a metabolite derived from HGA, is the common causative factor for both atypical myopathy in Europe and seasonal pasture myopathy in North America. Further studies are needed to confirm this hypothesis and to identify additional risk factors that may predispose horses to these myopathies [7–11].

3.3 Seasonality of atypical myopathy

Atypical myopathy in horses is more frequently reported in autumn for several reasons. In autumn, the trees shed their seeds, which can be dispersed by wind or water [12]. This increases the availability of sycamore seeds in pastures, making horses more likely to ingest them [13]. Alongside seed dispersal, autumn also marks a period of seedling growth for sycamore trees, as young seedlings and saplings of sycamore trees contain HGA [13]. The combination of fallen seeds and actively growing seedlings provides horses with additional opportunities for exposure to the toxin. Furthermore, horses may exhibit different grazing behaviours in autumn, for example, they might consume more fallen leaves, seeds, and seedlings when pasture grasses become less abundant or less palatable due to seasonal changes [14]. This altered grazing behaviour can increase the chances of horses ingesting sycamore seeds or seedlings. Finally, environmental conditions in autumn are characterized by wet and windy weather in many regions. Heavy rain, wind, or storms can disperse sycamore seeds over a wider area, including pastures where horses graze. This can result in an increased concentration of seeds in grazing areas, heightening the risk of ingestion [15].

4. Distribution and morphology of *Acer pseudoplatanus*

Acer pseudoplatanus, commonly known as sycamore, is native to Central and Southern Europe, ranging from the United Kingdom and France to the Caucasus Mountains in western Asia. It is also found in scattered populations in the northern Mediterranean region, the Balkan peninsula, and in parts of Turkey and Iran. The natural range of sycamore is divided into two distinct subpopulations: western and eastern. The western subpopulation is found in the United Kingdom, France, Germany, Switzerland, northern Italy, Austria, and parts of the Netherlands, Belgium, and Luxembourg. In the east, sycamore is found in the Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Greece, and parts of Turkey, Iran, and the former Yugoslavia [16].

Acer negundo, also known as box elder, has been linked to SPM in North America. The disease has been reported in the Western United States, including California, Idaho, Montana, Oregon, Utah, Washington, and Wyoming, as well as in the Canadian Provinces of British Columbia and Alberta. It has also been reported in the Midwest, including Michigan, Indiana, Illinois, Ohio, and Kentucky [1].

Figure 1. Acer pseudoplatanus, sycamore tree [17]

Acer pseudoplatanus as seen in **Figure 1.** [17] is a member of the family *Sapindaceae* and is a sizable deciduous tree, which prefers temperate climate and nutrient rich soil. It favours a slightly acidic or alkaline pH, and this species is often found side by side but dominating within soft wood deciduous forests. The tree cannot thrive in drought prone areas and prefers to grow under shaded conditions especially during its immature stage, which is why it succeeds in already present forests [1]. The sycamore maple has slowly been extending north of its native area since the seventeenth century, and now occupies 2267 of 10 km squares of the Atlas of the British Flora in the United Kingdom [18]. It is considered invasive in northern Norway and sometimes its removal is required from natural forests in Great Britain to prevent further spread [18].

The sycamore maple extends up to 20-30 meters in height, with the highest tree recorded reaching 40.50 meters in Germany. It has a trunk diameter of 60-80 centimetres, and can reach a circumference of 2 meters, the tree can live up to and more than 350-400 years old [19]. It is described as having a wide and dome like crown, which can sometimes exceed the height of the tree itself yet has a strong, deep-rooting system allowing it to withstand high wind knots easily despite the large crown [18].

Leaves of the sycamore maple **(Figure 2)** [20] measure up to 25 centimetres roughly and are made up of a large palmate with 5 pointed and veined lobed segments that change shape and size depending on the age and vigour of the shoot, a long reddish petiole and serrated leaf margins are present. The leaf is a dark green colour, with the underside of the leaf being gray-green and in autumn. The colour of the foliage varies between yellow and orange. Younger trees have a greyish-green and smooth bark, which becomes irregular and cracks into a scaly, quadrangle like shape that peels off and curls away at the edges as the tree grows older and the bark turns into a grey-brown colour, exposing a pale-brown-to-pinkish inner bark [1].

Figure 2. Morphology of an Acer pseudoplatanus leaf [20]

The sycamore is monoecious, meaning that both male and female organs are present but are separated on the same tree. The flowers of the sycamore (**Figure 3a)** [21] are most commonly hermaphroditic and cannot be recognized upon initial and brief inspection due to their small size. The colour of the flowers in the spring will be a yellow-green shade and will appear with 20-50 flowers on each stalk [21].

In early autumn the fruits, known as samaras (**Figure 3b)** begin to ripen and are easy to distinguish and recognize, as they hang in small groups and are paired, arranged at right angles and appear as an upside down "V" shape [22]. The size of the samaras can extend between three to five inches long (approximately 7.5 centimetres to 12.5 centimetres) [18]. The seed dispersion occurs via wind and when falling the samaras will spin giving a propeller appearance as they fall. The seeds can sometimes travel up to 4 kilometres depending on wind speed, but majority of the seeds as dispersed in a radius of 200 meters around the tree [19].

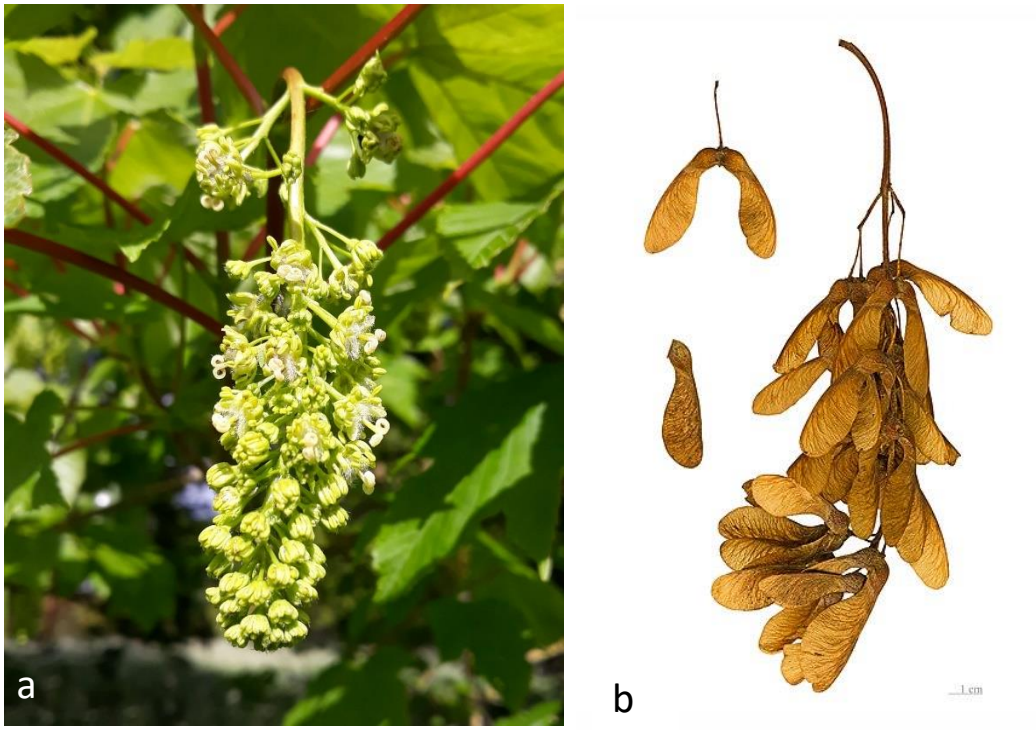

Figure 3. a) Acer pseudoplatanus in flower [21] b) Samara of Acer pseudoplatanus [22]

5. Pathogenesis of atypical myopathy

Atypical myopathy is a disease with an incompletely understood cause, characterized by acute muscle damage and hyperglycaemia [8]. It is associated with the ingestion of HGA, which is metabolized by the liver into toxic MCPA, after which it is eliminated in the urine [9]. MCPA binds to acyl-CoA dehydrogenase, which hinders the intracellular breakdown of long-chain fatty acids by damaging mitochondrial function. Variability in the rate of hypoglycin metabolism to MCPA may explain the differences in clinical symptoms, while the availability of co-factors like magnesium, pyridoxal phosphate, thiamine, and coenzyme A can influence an individual's susceptibility to the disease [10]. These four substances are all crucial co-factors in hypoglycin metabolism within the liver. Horses affected by AM may also show low serum carnitine levels, as MCPA simultaneously disrupts the carnitine-acyl-CoA transfer system [10].

Carnitine facilitates the transport of long-chain fatty acids into the mitochondria, allowing it to generate energy. Thus, when MCPA disrupts this pathway, it will further exacerbate the severity of clinical signs. This disruption will lead to the accumulation of fatty acids in both the mitochondria and cytosol, reducing the availability of free carnitine in the bloodstream. These low serum carnitine levels serve as a biochemical marker of AM, reflecting the disease's impact on fatty acid metabolism and mitochondrial function in affected horses. The microscopic effect can be visualized during histopathological analysis of lipid vesicles within muscle fibres using staining techniques like Oil Red O (ORO), which can assess intramuscular lipid storage within the cardiac muscle. Furthermore, type I myofibrils, found in postural, cardiac, and respiratory muscles, heavily rely on fatty acids for energy. The profound muscle weakness and respiratory difficulties seen in horses with atypical myopathy are attributed to disrupted lipid metabolism and reduced oxygen delivery in respiratory and cardiac muscle cells. This forces the body to rely more on anaerobic glycolysis, depleting muscle glycogen stores and resulting in lactic acid buildup [1, 9–11, 23].

6. Clinical signs of atypical myopathy

The clinical presentation of atypical myopathy can exhibit variations, closely resembling other equine myopathies. AM arises suddenly and unexpectedly with worsening clinical symptoms in a 72-hour time frame. This similarity between diseases and short time frame of disease development poses a challenge for veterinarians in making a precise and quick diagnosis solely based on clinical signs. Hence, a comprehensive medical history becomes imperative for facilitating an accurate diagnosis. In this context, key elements such as the horse's discipline, turnout practices, especially the presence or absence of pasture time, are essential pieces of information during anamnesis. Furthermore, when diagnosing atypical myopathy, it is crucial to inquire about the patient's feeding regimen, with a specific focus on determining the owner's awareness of any sycamore trees located in proximity to the stable or pasture where the equine resides. Below is a list of clinical symptoms that should be diligently monitored by both the owner and veterinarian [2, 6, 24, 25].

It is crucial to consider the potential occurrence of hyperthermia, which is characterized by a rectal temperature exceeding 43.8°C. Hyperthermia is often accompanied by spontaneous sweating, even in cooler conditions, as evident in some cases. Conversely, hypothermia, signified by a rectal temperature falling below 37.1°C, may manifest in place of hyperthermia in some instances [2]. Normothermia is also described from time to time. A prevailing sense of depression and lethargy is consistently a prominent and noteworthy clinical symptom. Dark red or chocolate coloured urine is often seen but it is important to note that it is not specific to AM, and is simply an indicator of muscle degeneration resulting in myoglobinuria which is also seen in other equine rhabdomyopathies, consequently the absence of pigmenturia does not disprove the presence of AM [9]. When performing rectal palpation, it is not uncommon to encounter a distended bladder, and at times, the presence of dry, mucous-covered faeces or colon impactions. These observations may give rise to colic symptoms or discomfort [2, 26].

Significant changes in the musculoskeletal system serve as distinctive indicators of various equine myopathies. AM symptoms may encompass stiffness, making movement and walking difficult or, in some cases, leading to a complete aversion to movement. Additionally, hindquarter muscle weakness may become evident, potentially progressing to a state of

recumbency, this is often a precursor to death. In certain instances, trembling and tremors may also manifest [2, 24, 25, 27].

Cardiovascular alterations may manifest as congested mucous membranes with a noticeable darkening of their natural colour. Additionally, there may be an elevation in heart rate, ranging from 40 to 68 beats per minute (BPM), and in rare cases arrythmias have been reported [2, 28]. Affected horses often exhibit respiratory issues upon admission, including tachypnoea and hyperventilation, likely arising from stress, pain and compensation for anaerobic respiration within muscle tissue. Dyspnoea may also develop due to weakened respiratory muscles, lateral recumbency could also worsen respiratory signs [2, 27].

7. Differential diagnosis

Equine atypical myopathy (AM) can easily resemble various other acute equine diseases. When diagnosing AM, it is important to differentiate it from several severe rhabdomyolysis syndromes, including, but not limited to, recurrent exertional rhabdomyolysis (RER), polysaccharide storage myopathy (PSSM), immune-mediated myopathy, clostridial myonecrosis, toxic myopathy caused by ingestion of ionophores or various species of toxic plants, nutritional myopathy, hyperkaliaemic periodic paralysis, malignant hyperthermia, and as-yet-unidentified lipid disorders [25, 29, 30].

It is also crucial to consider other conditions that can lead to endotoxemia or hypovolemic shock, particularly colic, as well as conditions that result in abnormal gait or recumbency, such as laminitis, neurological disease, hypocalcaemia, and pleuropneumonia. Additionally, it is worth noting that the acute form of equine grass sickness shares clinical signs, epidemiology, and associated risk factors with AM [2].

a. Recurrent exertional rhabdomyolysis and polysaccharide storage myopathy

In the case of recurrent exertional rhabdomyolysis, the clinical picture is similar in regards to general muscle weakness, tremors, and the characteristic dark or chocolate colored urine, although in AM the urine is reported to be slightly darker than seen in RER [2]. The main differential lies with a through anamnesis, as RER occurs most commonly if not exclusively following intense exercise [31]. RER is a condition related to the regulation of intracellular calcium, and it is prompted by excitement that can be induced during exercise [31]. Whilst in the case of AM, the affected animals were primarily pastured with minimal supplemental feeding, and the myopathy did not result from exertion. In contrast to recurrent exertional rhabdomyolysis, horses afflicted with AM succumbed within a short span of just a few days and mortality was reported to be anywhere from 40 to 100 percent, whereas mortality following exertional rhabdomyolysis was documented to be between 5 and 20 percent, depending on how treatment of horses with RER was managed by the primary veterinarian, as renal failure was reported to be the leading cause of death induced by RER [14, 15, 29].

PSSM is another disorder that comes under the exertional rhabdomyolysis (ER) category that is also characterized by muscle stiffness, tremors and pain in horses [32]. However, PSSM is

proven to be arising from a partial genetic background. PSSM1 is linked to a glycogen synthase 1 (GYS1) gene mutation that exists in over 20 horse breeds and is not associated with any specific pedigree. Horses only need one copy of this mutation to be affected, which leads to constant glycogen production in muscle cells. The excess glycogen is not efficiently utilized for energy during exercise due to disruption of glycogen metabolism, resulting in soreness and muscle cramping after light work [32, 33]. PSSM2, on the other hand, is not caused by a disorder relation to glycogen stores, but rather effecting the muscle fibrils themselves [34]. Overall, the similarities between AM and PSSM exhibit similar clinical signs induced by rhabdomyolysis in both instances, however PSSM can be induced when horses are overfed with grains or are insufficiently exercised resulting in glycogen build up and muscle cramping. In AM, history of being kept on pasture and limited feed is once again the critical distinguishing factor, it is essential to recognize and differentiate exertional rhabdomyolysis from atypical myopathy as that will drastically influence the course of treatment and management of these conditions [2, 25, 32–34].

b. Ionophore toxicosis

Ionophore toxicosis can be induced by the ingestion of even a limited amount of feed containing ionophores; a class of antibiotics commonly employed as feed additives in cattle and poultry diets, in particular the use of monensin and lasalocid, their purpose being enhancing feed efficiency and promoting weight gain. These compounds exert their effects by modifying rumen fermentation patterns, therefore gaining extensive utilization within the beef and poultry sectors due to their demonstrated capacity to not only to enhance feed efficiency but also effectively manage coccidiosis [35]. Horses exhibit a sensitivity to ionophores that is approximately tenfold greater than that of other species, thus if equine feed becomes inadvertently contaminated with ionophores or if horses consume cattle feed, it will often lead to toxicity. Manifestations of this toxicity encompass symptoms such as colic, prolonged loss of appetite whilst in AM appetite is seen to increase, rapid heartbeat associated with heart failure, respiratory distress, diarrhea, stiffness, muscle weakness, and a disinclination to stand. All of the symptoms can be concurrent with symptoms of AM, it is important to once again in history taking to note if the horse is kept with other animals in particular cattle and poultry and if so does the owner use ionophores as supplements in feed and if there a possibility of contamination of feed between species [2, 27, 30, 35, 36].

c. Toxic myopathy

Toxic myopathy can arise due to various plant species, some of which may manifest clinical signs resembling AM. These signs often include muscle weakness, tremors, and symptoms resembling colic. Among the plant species implicated in toxic myopathy are horse chestnut (*Aesculus hippocastanum*), black walnut (*Juglans nigra*), and red maple (*Acer rubrum*), among others [12, 37, 38].

Distinguishing between AM and toxic myopathy can pose a diagnostic challenge, as differentiation based solely on historical information may not always be feasible. The diagnostic approach primarily centres on the identification of potentially toxic agents present in the horse's environment, particularly in pastures. Consequently, owners should be questioned regarding the presence of specific plant species in proximity to the horse's grazing areas [25, 30, 37, 38].

To achieve a precise diagnosis and ascertain the causative agent, a comprehensive examination of the pasture may be warranted. In cases where the veterinarian possesses mobility, conducting an on-site evaluation of the pasture area can prove invaluable in the pursuit of an accurate diagnosis and the identification of the responsible toxic agent.

8. Diagnosis of AM

AM in horses is primarily diagnosed based on clinical signs, history, and specific laboratory tests. While blood and urine samples can provide valuable information to support the diagnosis, they are not always definitive on their own. Achieving a proper diagnosis of AM typically relies on the combination of all these factors.

a. Aspartate aminotransferase and creatine kinase levels

Elevated levels of AST and CK are frequently observed in cases of AM. These elevations stem from myocyte cell damage and subsequent degeneration resulting from the metabolism of HGA. The breakdown of muscle cells causes the release of intracellular constituents, including the enzymes CK and AST, into the circulatory system [2, 39, 40]. An effective diagnostic and prognostic approach involve analysis of both CK and AST level. Biochemical analysis of CK shows levels rapidly increasing to over 10,000 IU/L and occasionally exceeding 100,000 IU/L as the disease manifests and in accordance with the progression of severity of clinical signs. CK levels alone though cannot serve as a reliable prognostic factor, as it may only show a slight increase when measured shortly after onset of clinical signs, but a decrease in CK levels is usually seen as a good indicator towards improvement of the patient. Therefore, initially tests should be performed at an interval if 48-72 hours to provide a more comprehensive assessment [2, 39].

b. Myoglobinuria

Due to the breakdown of myocytes, myoglobinuria is a characteristic finding in the urine and is responsible for the dark red or chocolate brown color. The lack of myoglobinuria does not exclude AM as it is dependent on the severity of rhabdomyolysis at the time of the examination, similar to CK and AST levels. It should also be evaluated whether it is in fact myoglobinuria and not haemoglobinuria or haematuria causing the discoloration, therefore confirmation of myoglobin in urine or in a blood test is required [2, 39, 41].

c. Electrolytes abnormalities and acid-base disturbances

The electrolyte balance is significantly influenced in cases of atypical myopathy (AM), with sodium, potassium, chloride, magnesium, and calcium being the primary ions affected [26]. Predominantly, hypocalcaemia, hyponatremia, and hypochloraemia are the prevailing electrolyte disturbances observed, although less frequently, hypernatremia and hyperkalaemia may also manifest [4, 26, 41]. Muscle damage incurred in AM leads to the release of

intracellular potassium and magnesium ions, resulting in the observed elevation of these ions. Hyperkalaemia poses a concern as it can give rise to irregular heart rhythms, contributing to reported instances of arrhythmias [28]. As myocyte degradation progresses and necrosis ensues, lactic acidosis becomes prevalent due to impaired oxygen delivery, prompting myocytes to shift to anaerobic metabolism. This metabolic shift results in the production of lactic acid as a byproduct, which subsequently enters the bloodstream. Concurrently, respiratory alkalosis may develop alongside lactic acidosis. As previously noted, hyperventilation often presents as one of the initial clinical signs of AM. It serves as a compensatory response to both lactic acidosis and diminished oxygen levels within the bloodstream. Stress and the fact that the primary muscle groups affected in AM are postural and respiratory contribute to hyperventilation. The body's aim is to mitigate oxygen stress by reducing blood carbon dioxide levels and counteract lactic acidosis, ultimately striving to elevate the blood pH [2, 19, 27, 40, 41].

d. HGA and MCPA-conjugate detection

HGA and MCPA conjugates can be detected in the blood and urine samples of horses, in one study horses affected with AM were seen to have higher concentrations of HGA and MCPA conjugates than that of co-grazing horses from the same pastures and control horses. HGA concentrations in horses ranged from 166-652 nmol/L, with the highest concentration found in horses that succumbed to AM or were euthanized as a result of the disease. This study suggests that early detection of HGA in co-grazing horses might be a promising step in prophylaxis against atypical myopathy. The study also discovered that healthy co-grazing horses on AM-pastures have higher serum and urine concentrations compared to control horses, but lower concentrations compared to diseased horses, therefore linking HGA intoxication to disease outbreak. Concentrations of HGA and MCPA were analysed using mass spectrometry [9].

9. Treatment

Therapeutic management of AM relies on symptomatic care, guided by clinical observation and laboratory assessments of blood and urine samples. The treatment strategy encompasses several critical facets. This involves rectifying acid-base imbalances to restore normal pH levels in the body. Therapy also aims to facilitate the elimination of HGA and its metabolites from the patient's system, a vital step in the recovery process [9, 42, 43].

Furthermore, comprehensive support for mitochondrial function is essential, particularly during the oxidative stress provoked by AM. The provision of supplementary energy sources is of high importance, with a specific focus on the respiratory and postural muscle groups [2], which are notably affected. Analgesic measures are implemented to manage pain, enhancing the horse's comfort throughout the disease course. Finally, there is a dedicated effort to prevent further injury to the affected patients, encompassing strategies to minimize complications associated with AM. These multifaceted interventions are tailored to alleviate clinical signs and mitigate the impact of AM on affected horses [9, 42, 43].

a. Emergency care and fluid therapy

If the horse is recumbent and unable to stand, it is not advisable to move or transport it to a clinic. Such actions can exacerbate the existing myopathy and electrolyte imbalance. Ideally, treatment should be initiated at home, preferably within a stable environment, especially if the horse is experiencing hypothermia. In cases of hypothermia, it is important to consider using heat lamps, blankets, and administering warmed intravenous fluids to help raise the horse's body temperature. For recumbent horses, it is recommended to provide deep bedding and periodically turn them every few hours. This practice helps minimize muscle damage while reducing the risk of respiratory and cardiovascular complications. Placing these horses into slings is not a recommended course of action [11, 26, 44].

Fluid therapy constitutes a pivotal component in the treatment of AM. Adequate hydration serves multiple critical purposes, including facilitating renal support, as one study has noted development of renal tubular necrosis [45], and encouraging renal filtration. This assumes high importance because myoglobin levels in the bloodstream surge as the disease advances, and without effective patient rehydration, the potential for subsequent renal failure increases [26].

Fluid administration also plays a pivotal role in rectifying acid-base imbalances and promoting the elimination of HGA and its metabolites [26].

In one illustrative study, two Haflinger horses received saline, Ringer's solution, and Duphalyte as part of fluid therapy, alongside additional medications; regrettably, one of the horses did not survive. Conversely, in the same study, a Hucul pony received Jecuplex, a solution composed of essential amino acids and vitamins, and successfully recovered. Details of concurrent medication administration were not recorded in this instance [43].

The choice of fluid therapy is further tailored to individual cases, guided by the specific electrolyte abnormalities identified during initial presentation [26]. Additionally, the administration of 5% glucose or dextrose-containing solutions may be beneficial, but this should only be undertaken if regular blood glucose monitoring is feasible. These solutions aim to provide an energy source to reinitiate aerobic metabolism and correct lactic acidosis. When indicated by rectal palpation findings of a distended bladder, catheterization may be necessary to facilitate proper urine excretion. Typically, fluid therapy is continued until the correction of acid-base imbalances and the attainment of yellow urine, signifying renal function restoration [2, 26, 42, 43].

b. Analgesia and cardiac monitoring

In cases where a horse is recumbent, the administration of analgesics is crucial. Pain relief can potentially enable the horse to stand, alleviating stress on the respiratory and cardiovascular systems. However, it is imperative to limit the horse's movement as much as possible, ideally confining it to a stable. When selecting analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) like meloxicam and ketoprofen are preferred over phenylbutazone and flunixin due to their greater safety profile and effectiveness for musculoskeletal pain associated with AM. Opiates are typically avoided because their side effects can exacerbate the clinical signs observed in AM [26, 42, 46, 47].

In cases where a horse exhibits tachycardia, it is essential to assess circulating volume and cardiac function, considering more intensive pain management if necessary. The administration of digoxin may be considered for horses with reduced myocardial function, as it has a positive inotropic effect and can improve renal blood flow. If arrhythmias develop, electrolytes should

be checked and corrected if imbalanced, and in severe cases, anti-arrhythmic drugs should be contemplated [26, 45, 48].

c. Vitamin supplementation and gastrointestinal management

The supplementation of vitamin E, vitamin B2 (riboflavin), and selenium serves a crucial role in the management of AM. Vitamin E and selenium function as antioxidants, shielding cells and tissues from oxidative damage caused by HGA. Simultaneously, riboflavin complements this antioxidant defense by supporting the production of essential antioxidant molecules within the body. The combined use of these three substances contributes significantly to the recovery process in AM cases. Moreover, they play a key role in preventing further myocyte damage, aiding the reduction of further rhabdomyolysis [2, 39, 42, 45].

Activated charcoal serves the purpose of binding HGA within the gastrointestinal tract [49]. By doing so, it diminishes toxin absorption. The timing of samaras ingestion is a key factor that guides the veterinarian's decision regarding the use of activated charcoal [42]. Liquid paraffin can also be used as a laxative, although its administration warrants consideration. The primary concern is whether emptying the gut and depleting the horse of nutrients is the most appropriate course of action. Given the essential need for a continuous energy source in AM cases, an approach of administering liquid paraffin immediately after toxin ingestion may prove more beneficial [42, 45].

It is imperative to avoid fasting horses with AM at all costs. Instead, the diet should consist of foods that are high in carbohydrates and low in lipids. In the context of AM's pathophysiology, horses affected by this condition cannot efficiently metabolize fatty acids and often experience hyperlipemia. Therefore, high lipid foods pose a significant risk, potentially exacerbating the existing metabolic imbalance [26, 42].

To address these nutritional needs, it is advisable to provide carbohydrate-rich foods with a high glycaemic index, along with dietary fibers, including high-quality hay and alfalfa. Grains and concentrates should be restricted in the diet. Additionally, offering the horse small, frequent meals throughout the day is preferred over providing one or two large meals. Ensuring adequate nutritional support is essential to counteract the negative energy balance associated with AM [2, 26, 39, 42, 50].

10. Case study review

A case report was done at the University of veterinary medicine and pharmacy in Slovakia of a 2-year-old Haflinger colt horse that presented with clinical signs of AM toxicosis, it was found recumbent in the pasture. The horse displayed bilateral nasal discharge, cough and lethargy. Multiple attempts were done to coax the colt into standing, and once successful, the horse was subsequently taken to the university clinic. Once at the clinic the horse was once again in lateral recumbency and reactive to a minimal degree, other clinical signs observed were an increased respiratory rate, a temperature of 36 °C and congested mucous membranes with a capillary refill time of 4 seconds. The cardiac exam revealed normal auscultation of the heart but decreased gut sounds were noted. Subsequently laboratory tests were performed, blood lactate was elevated signifying metabolic acidosis and the biochemical profile showed slight increase in glucose concentration, and decreased levels of calcium. Further abnormal findings were an elevation of CK, AST and lactate dehydrogenase (LDH). Electrolytes and haematology were both noted to be within normal parameters. The horse was moved to the stall and was able to stand, but respiratory distress, weakness and abnormal posture was documented. Urine discoloration was seen signifying myoglobinuria and initially urination was spontaneous but ultimately a urinary catheter had to be placed once the horse was recumbent once more. The owner informed that the horse had not exercised recently and mentioned that no sycamore trees were seen on or in the vicinity of the pasture. Intravenous therapy was administered, which included duphalyte, flunixin meglumine for pain relief, along with oxytocin and N-butylscopolammonium bromide. Despite treatment the owner agreed to euthanasia due to the worsening status of the horse. Whole blood was sent to a laboratory to be analysed and an elevation of HGA and MCPA was documented confirming AM [51].

The website Right Horse Right Home has a section called ‘Atypical Myopathy – Sufferers and Survivors’, this website allows owners in the United Kingdom to give accounts of their experience with the disease and the signs they have witnessed. In February 2023 one owner discovered their 6-year-old Connemara horse, in the pasture with a reluctancy to move but standing upright. The horse was reported to be exercised up to 5 times a week. It was seen with a loss of appetite, a mild elevation in rectal temperature and dark pungent urine. A veterinarian was called to the site and colic was suspected, without the usual colic signifiers such as rolling. Nonetheless, the horse was treated for colic. Upon further examination decreased gut sounds

were noted as well as an increased heart rate at 60 BPM. Initially the veterinary staff did not suspect AM as February was not the usual season for when AM cases are seen. However, blood was collected for analysis that revealed an increase in muscle enzymes, so immediate treatment was warranted. The horse was brought to the clinic where intravenous fluid was then administered as now AM was suspected to be the cause. After fluid administration, the bloodwork was done again showing inclination towards normalization. Unfortunately as time went by the horse developed signs of neurological deficits and the decision was made to euthanize [52].

Another case from the same website reported that their Irish sport horse went lame on the way back home after hacking with her owner in October. Upon arrival home the horse was seen to be sweating profusely even though according to the owner there was no intense exercise done during the hack. Further monitoring by the owner revealed continuation of sweating and excessive shivering, so the horse was double rugged at the time and the vet was called out with a suspicion of colic, and as such medication to treat colic was administered, this included Buscopan and unknown pain relief. Blood was collected for diagnostics. The following morning the horse could walk but with intense stiffness and urine 'the color of blood' was reported by the owner. Blood work was returned after being sent to the Royal Veterinary College in London and revealed extreme elevation of muscle enzymes. The horse was then admitted to the veterinary clinic and was hospitalized for a period of 4-5 weeks after which she was discharged when muscle enzymes levels were seen to normalize. No sycamore seeds were documented by the owner on pasture, but AM is still suspected to be the cause due to the seasonality of when this horse presented and the high wind speed that was reported at the time [53].

11. Conclusion

After examining atypical myopathy in this review, it is reasonable to conclude that, according to the existing evidence and pathogenesis analysis, it is highly likely that the clinical signs observed in equine atypical myopathy are a result of the toxin HGA, which is found in the samaras of *Acer pseudoplatanus* trees in Europe. As a result, owners of equids should remain vigilant about the potential presence of sycamore trees in or around their pastures. This vigilance is particularly crucial after windy or stormy conditions, notably during autumn when samaras can disperse over long distances. It is advisable to inspect the pastures or grazing areas accessible to horses in these situations. To prevent intoxication, providing adequate feed to horses on pasture becomes essential, as horses may be more inclined to ingest the seedlings when pasture feed becomes scarce during the cooler autumn weather. Hence, it is imperative for owners to consider factors such as seasonality, the horses' grazing patterns, and the availability of supplementary feed when aiming to prevent atypical myopathy. Veterinarians should also consider the seasonal prevalence of equine atypical myopathy, being aware that it may be more common in certain seasons than in others. However, it is essential to bear in mind that although rare, the disease can also develop during seasons outside of the more common ones.

Thoroughly documenting a patient's medical history, as previously emphasized, emerges as a pivotal aspect. Distinguishing atypical myopathy from other equine muscle disorders is important to ensure timely and appropriate treatment for the affected horses, as time is of the essence when dealing with AM. Crucial questions to pose to horse owners center around their memory of the horse’s recent workload, enabling differentiation from exertional rhabdomyolysis. It is also essential to ascertain when they initially observed symptoms, allowing us to distinguish between acute and chronic cases, considering the typically abrupt onset of atypical myopathy. An assessment of the horse's grazing habits must be done and asking owners what other animals are potentially present in the horse’s living environment as this can help us gauge the potential for ionophore toxicosis as a differential diagnosis.

As discussed in chapter 3, clinical signs pose a diagnostic challenge alone as the disease mimics other myopathies and colic. Key indicators to look out for are dark brown or red urine, abnormal rectal temperature readings, limb stiffness, sudden recumbency, and reluctancy to stand.

Diagnostic steps that should be taken include a comprehensive physical evaluation, rectal examination, and an ultrasound to rule out acute colic and to assess cardiac function. Blood work analysis should be done, with a particular focus on a full biochemical profile to check for markers like lactate, creatine kinase and aspartate aminotransferase electrolyte levels of the patient. An intravenous catheter should be placed, and infusion therapy should be started, with the choice of therapy contingent on the observed electrolyte abnormalities, left to the discretion of the attending veterinarian. Collecting a urine sample is recommended, especially if the owner describes the urine as appearing 'bloody' or dark. This aids in confirming or ruling out myoglobinuria through urinalysis. If clinical signs and blood analysis suggest AM even when urine appears normal, continuous urine monitoring is advised. Assessing and addressing glucose fluctuations is vital to prevent energy depletion and further electrolyte imbalances due to anaerobic respiration. For those with the financial means, a definitive diagnosis of AM can be obtained by sending blood or urine samples for mass spectrometry analysis to detect HGA and MCPA conjugates. It is also important to recommend treatment for pasture mates, even if they display no clinical symptoms. Immediate removal of animals from pasture is advisable until AM is either confirmed or ruled out.

In summary, the key takeaway is that there is currently no cure for equine atypical myopathy, and the primary approach to treatment involves symptomatic management. Effective management of each abnormal parameter is crucial when addressing this condition. Gathering a patient's history is equally significant in importance as the actual treatment of the patient. Informing the owners of the severity of AM as well as encouraging them to maintain constant vigilance, particularly when it comes to the quality of the pasture should be advised. While veterinarians should adopt a methodical, step-by-step approach to diagnose and treat such cases. Advancement in veterinary medicine could potentially enable more cost-effective detection of HGA in both serum and urine. Confirming HGA as the causative agent found in *Acer pseudoplatanus* resulting in equine atypical myopathy may open the door to the development of effective treatment options, reducing the reliance on symptomatic treatments alone.

12. References

1. Valberg SJ, Sponseller BT, Hegeman AD, Earing J, Bender JB, Martinson KL, Patterson SE, 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 45:419–426. https://doi.org/10.1111/j.2042-3306.2012.00684.x

2. Votion D-M (2012) The Story of Equine Atypical Myopathy: A Review from the Beginning to a Possible End. ISRN Veterinary Science 2012:. https://doi.org/10.5402/2012/281018

3. Van Galen G, Amory H, Busschers E, Cassart D, De Bruijn M, Gerber V, Keen J, Lefere L, Pitel CM, Marr C, Müller J-MV, Pineau X, Saegerman C, Sandersen C, Serteyn D, Torfs S, Unger L, Verwilghen D, Votion D-M (2010) European outbreak of atypical myopathy in the autumn 2009. J Vet Emerg Crit Care (San Antonio) 20:528–532. https://doi.org/10.1111/j.1476-4431.2010.00574.x

4. Votion D-M, Linden A, Delguste C, Amory H, Thiry E, Engels P, van Galen G, Navet R, Sluse F, Serteyn D, Saegerman C (2009) Atypical myopathy in grazing horses: a first exploratory data analysis. Vet J 180:77–87. https://doi.org/10.1016/j.tvjl.2008.01.016

5. Equine atypical myopathy in the UK: Epidemiological characteristics of cases reported from 2011 to 2015 and factors associated with survival - González-Medina - 2017 - Equine Veterinary Journal - Wiley Online Library. https://beva.onlinelibrary.wiley.com/doi/abs/10.1111/evj.12694. Accessed 3 Oct 2023

6. Atypical Myopathy. https://en.audevard.com/horse-health-space/atypical-myopathy. Accessed 4 Oct 2023

7. Votion D-M, van Galen G, Sweetman L, Boemer F, de Tullio P, Dopagne C, Lefère L, Mouithys-Mickalad A, Patarin F, Rouxhet S, van Loon G, Serteyn D, Sponseller BT, Valberg SJ (2014) Identification of methylenecyclopropyl acetic acid in serum of European horses with atypical myopathy. Equine Vet J 46:146–149. https://doi.org/10.1111/evj.12117

8. Von Holt null, Chang J, Von Holt null, Boehm H (1964) METABOLISM AND METABOLIC EFFECTS OF HYPOGLYCIN. Biochim Biophys Acta 90:611–613. https://doi.org/10.1016/0304-4165(64)90242-9

9. Bochnia M, Ziegler J, Sander J, Uhlig A, Schaefer S, Vollstedt S, Glatter M, Abel S, Recknagel S, Schusser GF, Wensch-Dorendorf M, 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:e0136785. https://doi.org/10.1371/journal.pone.0136785

10. Naylor R (2016) Atypical myopathy – insights on pathogenesis. Equine Veterinary Journal 48:401–402. https://doi.org/10.1111/evj.12562

11. Gonzalez-Medina S (2015) Update on the cause of equine atypical myopathy. Vet Rec 176:143–145. https://doi.org/10.1136/vr.h414

12. van der Kolk JH, Wijnberg ID, Westermann CM, Dorland L, de Sain-van der Velden MGM, Kranenburg LC, Duran M, Dijkstra JA, van der Lugt JJ, Wanders RJA, Gruys E (2010) Equine acquired multiple acyl-CoA dehydrogenase deficiency (MADD) in 14 horses associated with

ingestion of Maple leaves (Acer pseudoplatanus) covered with European tar spot (Rhytisma acerinum). Mol Genet Metab 101:289–291. https://doi.org/10.1016/j.ymgme.2010.06.019

13. Żuraw A, Dietert K, Kühnel S, Sander J, Klopfleisch R (2016) Equine atypical myopathy caused by hypoglycin A intoxication associated with ingestion of sycamore maple tree seeds. Equine Vet J 48:418–421. https://doi.org/10.1111/evj.12460

14. McGowan CM, Fordham T, Christley RM (2002) Incidence and risk factors for exertional rhabdomyolysis in thoroughbred racehorses in the United Kingdom. Vet Rec 151:623–626. https://doi.org/10.1136/vr.151.21.623

15. MacLeay JM, Sorum SA, Valberg SJ, Marsh WE, Sorum MD (1999) Epidemiologic analysis of factors influencing exertional rhabdomyolysis in Thoroughbreds. Am J Vet Res 60:1562–1566

16. Acer pseudoplatanus. In: Forest Research. https://www.forestresearch.gov.uk/tools-and-resources/seed-storage/acer-pseudoplatanus/. Accessed 3 Oct 2023

17. Acer pseudoplatanus, Sycamore, identification guide. https://www.first-nature.com/trees/acer-pseudoplatanus.php. Accessed 4 Oct 2023

18. Binggeli P, Rushton B (1999) Sycamore and Ash A Review of Aspects Relevant to Irish Forestry

19. European Atlas of Forest Tree Species | PDF | Oak | European Union. In: Scribd. https://www.scribd.com/document/342165852/European-Atlas-of-Forest-Tree-Species. Accessed 3 Oct 2023

20. Sycamore Maple | Acer pseudoplatanus. https://www.tree-guide.com/sycamore-maple. Accessed 4 Oct 2023

21. Acer pseudoplatanus - Trees and Shrubs Online. https://www.treesandshrubsonline.org/articles/acer/acer-pseudoplatanus/. Accessed 4 Oct 2023

22. Q422, Viaf: 131004808, Isni: 0000 0001 2158 3469, Sudoc: 028667107, Bnf: 120455376, M7013 M File:Acer pseudoplatanus MHNT.BOT.2004.0.461.jpg - Wikipedia. https://commons.wikimedia.org/wiki/File:Acer_pseudoplatanus_MHNT.BOT.2004.0.461.jpg. Accessed 4 Oct 2023

23. Von Holt C (1966) Methylenecyclopropaneacetic acid, a metabolite of hypoglycin. Biochim Biophys Acta 125:1–10. https://doi.org/10.1016/0005-2760(66)90138-x

24. Atypical Myopathy (Sycamore Poisoning) - Scott Dunn's Equine Clinic. https://scott-dunns.co.uk/equine-advice/ailments-and-diseases/equine-atypical-myopathy/. Accessed 8 Oct 2023

25. Atypical Myopathy Fact File - Fact Files - Information and Advice - RVC Equine - Royal Veterinary College, RVC. https://www.rvc.ac.uk/equine-vet/information-and-advice/fact-files/atypical-myopathy#panel-causes. Accessed 8 Oct 2023

26. Van Galen G, Votion D-M (2013) 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: Management of atypical

myopathy cases: Part 2. Equine Veterinary Education 25:308–314. https://doi.org/10.1111/j.2042-3292.2012.00441.x

27. Traumatic, Toxic, and Anesthetic Myopathies in Horses - Musculoskeletal System. In: MSD Veterinary Manual. https://www.msdvetmanual.com/musculoskeletal-system/myopathies-in-horses/traumatic,-toxic,-and-anesthetic-myopathies-in-horses. Accessed 8 Oct 2023

28. Verheyen T, Decloedt A, De Clercq D, van Loon G (2012) Cardiac Changes in Horses with Atypical Myopathy. Journal of Veterinary Internal Medicine 26:1019–1026. https://doi.org/10.1111/j.1939-1676.2012.00945.x

29. Exertional Rhabdomyolysis in Horses. https://www.petmd.com/horse/conditions/musculoskeletal/exertional-rhabdomyolysis-horses. Accessed 8 Oct 2023

30. Muscle Disorders in Horses - Horse Owners. In: Merck Veterinary Manual. https://www.merckvetmanual.com/horse-owners/bone,-joint,-and-muscle-disorders-in-horses/muscle-disorders-in-horses. Accessed 8 Oct 2023

31. Equine Exertional Rhabdomyolysis: Management of Sporadic Exertional Rhabdomyolysis | AAEP. https://aaep.org/issue/equine-exertional-rhabdomyolysis-management-sporadic-exertional-rhabdomyolysis. Accessed 8 Oct 2023

32. (2019) PSSM in horses: A summary of the scientific facts - News - Utrecht University. https://www.uu.nl/en/news/pssm-in-horses-a-summary-of-the-scientific-facts. Accessed 8 Oct 2023

33. Polysaccharide storage myopathy (PSSM) in horses. https://extension.umn.edu/horse-health/polysaccharide-storage-myopathy-pssm. Accessed 8 Oct 2023

34. GmbH WD PSSM 2 - Polysaccharid-Speicher-Myopathie Typ 2. https://www.hoeveler.com/gut-zu-wissen/artikel/pssm-2-polysaccharid-speicher-myopathie-typ-2.html. Accessed 8 Oct 2023

35. Ionophore - an overview | ScienceDirect Topics. https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/ionophore. Accessed 8 Oct 2023

36. Ony EE (2012) Ionophore Toxicity in Horses. In: Kentucky Equine Research. https://34.70.138.44/equinews/ionophore-toxicity-horses/. Accessed 8 Oct 2023

37. Horse chestnut Poisoning in Horses. https://horsedvm.com/poisonous/horse-chestnut. Accessed 9 Oct 2023

38. Black walnut: a toxic horse bedding. https://extension.umn.edu/horse-pastures-and-facilities/black-walnut-toxic-horse-bedding. Accessed 9 Oct 2023

39. Votion D-M, Serteyn D (2008) Equine atypical myopathy: a review. Vet J 178:185–190. https://doi.org/10.1016/j.tvjl.2008.02.004

40. Westermann CM, Dorland L, van Diggelen OP, Schoonderwoerd K, Bierau J, Waterham HR, van der Kolk JH (2011) Decreased oxidative phosphorylation and PGAM deficiency in horses

suffering from atypical myopathy associated with acquired MADD. Mol Genet Metab 104:273–278. https://doi.org/10.1016/j.ymgme.2011.07.022

41. Whitwell KE, Harris P, Farrington PG (1988) Atypical myoglobinuria: an acute myopathy in grazing horses. Equine Vet J 20:357–363. https://doi.org/10.1111/j.2042-3306.1988.tb01545.x

42. Evidence-based therapy for atypical myopathy in horses - Fabius - 2018 - Equine Veterinary Education - Wiley Online Library. https://beva.onlinelibrary.wiley.com/doi/abs/10.1111/eve.12734. Accessed 10 Oct 2023

43. Karlíková R, Široká J, Jahn P, Friedecký D, Gardlo A, Janečková H, Hrdinová F, Drábková Z, Adam T (2016) Equine atypical myopathy: A metabolic study. Vet J 216:125–132. https://doi.org/10.1016/j.tvjl.2016.07.015

44. Brandt K, Hinrichs U, Glitz F, Landes E, Schulze C, Deegen E, Pohlenz J, Coenen M (1997) Atypical myoglobinuria in grazing horses. Pferdeheilkunde 13:27–34. https://doi.org/10.21836/PEM19970104

45. Galen GV, Serteyn D, Amory H, Votion DM (2008) Atypical myopathy: New insights into the pathophysiology, prevention and management of the condition. Equine Veterinary Education 20:234–238. https://doi.org/10.2746/095777308X299103

46. D'Arcy-Moskwa E, Noble GK, Weston LA, Boston R, Raidal SL (2012) Effects of meloxicam and phenylbutazone on equine gastric mucosal permeability. J Vet Intern Med 26:1494–1499. https://doi.org/10.1111/j.1939-1676.2012.01004.x

47. Comparative efficacy of oral meloxicam and phenylbutazone in 2 experimental pain models in the horse - PubMed. https://pubmed.ncbi.nlm.nih.gov/28216685/. Accessed 10 Oct 2023

48. Muir WW, McGuirk SM (1985) Pharmacology and pharmacokinetics of drugs used to treat cardiac disease in horses. Vet Clin North Am Equine Pract 1:335–352. https://doi.org/10.1016/s0749-0739(17)30759-9

49. Essential Drug Data for Rational Therapy in Veterinary Practice by Kingsley Eghianruwa - Ebook | Scribd. https://www.scribd.com/book/387426290/Essential-Drug-Data-for-Rational-Therapy-in-Veterinary-Practice. Accessed 10 Oct 2023

50. (PDF) 58519_Metabolisme_dan_Nutrition[2].pdf | Vira Alifta - Academia.edu. https://www.academia.edu/37619236/58519_Metabolisme_dan_Nutrition_2_pdf. Accessed 10 Oct 2023

51. Pettenello M, Čriepoková Z, Rovňanová N, Kostolániová V, Valocký I, Hura V (2023) Atypical myopathy in a horse: first confirmed case in Slovakia. Acta Vet Brno 92:267–270. https://doi.org/10.2754/avb202392030267

52. Rebecca (2023) Atypical Myopathy - Connor - Rebecca's Story. In: Right Horse Right Home. https://www.righthorserighthome.co.uk/atypical-myopathy-connor-rebeccas-story/. Accessed 11 Oct 2023

53. Rebecca (2023) Atypical Myopathy - Jane’s Story - A Survivor. In: Right Horse Right Home. https://www.righthorserighthome.co.uk/atypical-myopathy-janes-story-a-survivor/. Accessed 11 Oct 2023

Acknowledgments

I would like to acknowledge and thank my thesis supervisor Daniel Cserhalmi and the botany department for supporting my work on this paper throughout the last couple of months, considering as always, everything I sent was done at the last minute.

I would also like to thank my family, in particular my mum Anna, who despite everything that these last five and a half years have thrown at me has always given me the opportunity and support I needed to make it through this degree. Furthermore, another person worth mentioning is my grandad who believed in me from the start.

Finally I would like to thank my friends and David, for being a constant presence in my life this last year, and during this degree, I'm not quite sure where I would be without them at this moment in time.

Thesis progress report for veterinary students

Name of student: Evgeniya Boytsova

Neptun code of the student: QE0CWP

Name and title of the supervisor: Dr. Cserhalmi Dániel, associate professor

Department: Botany

Thesis title: Equine Atypical Myopathy as a result of sycamore toxicosis

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	3	11	Permission to start thesis – approved topic	
2.	2023	3	20	Chapters review	
3.	2023	5	8	Structure review	
4.	2023	5	25	References + progress check	
5.	2023	6	2	Progress check	

Grade achieved at the end of the first semester: 5

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	9	15	Structural edits + chapter order edits	
2.	2023	9	29	Review new final chapters	
3.	2023	10	16	Confirm edits made by supervisor	
4.	2023	10	31	Final edits before uploading	
5.	2023	11	7	Plagarism check okay – proceed to upload	

Grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....

signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in 8/11/2023

I hereby confirm that I am familiar with the content of the thesis entitled

……...Atypical Myopathy as a result of Sycamore toxicosis……
……..

……..……..

…….. written by ……Evgeniya Boytsova ……..……..

(student name) which I deem suitable for submission and defence.

Date: Budapest, …14…….day……11……..month ……2023……year

……Daniel Cserhalmi……

……. Supervisor name and signature

……Botany department ……

……. Department

ÁLLATORVOSTUDOMÁNYI EGYETEM
Növénytani Tanszék
1787
BUDAPEST