

Satellite Article

Atypical myopathy: New insights into the pathophysiology, prevention and management of the condition

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Summary

Atypical myopathy (AM) is a frequently fatal seasonal pasture myopathy that has emerged in several European Countries in recent years. Currently, the aetiology of AM is unknown but recent surveys of confirmed cases have led to new insights into the pathophysiology, prevention and management of the condition.

Introduction

Sherlock and Mair (2008) described a filly affected with atypical myoglobinuria. This syndrome of a highly fatal, acute myopathy affecting grazing horses was initially named 'atypical myoglobinuria' (Anon 1985). However, since myoglobinuria is only one of the possible clinical signs of the condition, the name atypical myopathy (AM) is now preferred (Votion *et al.* 2004).

Atypical myopathy has been reported sporadically since the beginning of the 20th century in various parts of the world (Votion *et al.* 2004), but mainly in the UK. Since the new millennium, AM has been recognised in an increasing number of countries (Delguste *et al.* 2002; Gerber *et al.* 2006; van der Kolk 2006; Palencia and Rivero 2007) showing the emerging character of the condition. A similar condition has also been recognised in the USA (Finno *et al.* 2006). In Belgium and France, large outbreaks of AM are now encountered at regular intervals (Puyalto-Moussu *et al.* 2004; Votion *et al.* 2007).

Epidemiology

According to a large case report (Votion *et al.* 2007), AM seems to occur in horses being on pasture for at least one week. However, horses can still develop the condition in the following days after being placed in a box (G. van Galen, unpublished data).

The condition is reported to occur on bare, sloping pastures with trees. Most of the grazed pastures where AM occurs contain humid areas and are crossed or being bordered by a watercourse (Votion *et al.* 2007).

Affected horses are often young, unbroken and in good body condition, however older horses have also been affected (Brandt *et al.* 1997; Puyalto-Moussu *et al.* 2004; Votion *et al.* 2004, 2007). Recently, even a donkey and a zebra were highly suspected to suffer from AM (reported cases via the Atypical Myopathy Alert Group; Anon 2006).

The condition does not seem to be contagious, but it is usually reported as outbreaks since particular environmental characteristics and specific weather conditions predispose to AM. The climatic conditions favouring AM are little sunshine, cool temperature without heavy frost, heavy rainfall or humidity, and strong winds (Hosie *et al.* 1986; Whitwell *et al.* 1988; Votion *et al.* 2007). These particular conditions lead to seasonal occurrence (i.e. the majority of cases are observed in autumn and some in spring; Votion *et al.* 2007). It is postulated that the observed climate changes of recent years contribute to the increasing number of cases recorded.

Aetiology

At present, the aetiology of AM remains unknown but several causes have been considered. Toxic products, such as ionophores, herbicides, weed killers, nitrates and nitrites have been incriminated. However, testing for these products yielded negative results (Whitwell *et al.* 1988; Brandt *et al.* 1997). Phytotoxins have also been suspected, but plants known to be toxic for horses or other animals were not consistently present in the pastures of affected horses and/or were previously identified to cause other clinical signs than rhabdomyolysis (Hosie *et al.* 1986; Brandt *et al.* 1997; Puyalto-Moussu *et al.* 2004; Votion *et al.* 2007). No evidence of viral infections was found in cases with AM (Whitwell *et al.* 1988; Brandt *et al.* 1997; Delguste *et al.* 2002). Mycotoxins could be involved as they are known to have potential toxic effects in equids

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(Osweiler 2001). The recently described human fatal myopathic condition caused by mycotoxins supports this hypothesis (Bedry *et al.* 2001). Moreover, fungal growth and mycotoxin production depends on specific climatic conditions similar to those favouring AM. Other researchers have proposed clostridial toxins as a cause of AM (Delguste *et al.* 2002; Gerber *et al.* 2006). Unfortunately, so far no research has been able to confirm either mycotoxins or *Clostridium* spp. as the causative agent. Selenium or vitamin E deficiency can lead to a nutritional myopathy, often resembling AM. Antioxidant status of AM cases was variable (Hosie *et al.* 1986; Whitwell *et al.* 1988; Brandt *et al.* 1997), but nutritional myopathy is not thought to be the cause of AM since supplementation and treatment with selenium and vitamin E rarely improve the condition. However, these important antioxidants may have a protective role against a potential oxidative stress encountered in the pathophysiological process of AM.

Pathogenesis

The myodegenerative process of AM affects more selectively oxidative (i.e. the slow-twitch or *type I* fibres mainly found in postural and respiratory muscles) rather than glycolytic fibres (i.e. the fast twitch or *type II* fibres predominantly found in locomotory muscles) (Brandt *et al.* 1997; Cassart *et al.* 2007; Palencia and Rivero 2007). In addition, increased lipid storage is prominent in *type I* fibres (Cassart *et al.* 2007). These observations, along with no abnormal glycogen or polysaccharide accumulation, suggested an impaired oxidative metabolism and a preserved glycolytic pathway (Cassart *et al.* 2007). In addition, a central role of the mitochondria in the pathogenesis of AM was suggested by the observation of mitochondrial ultrastructural changes (Cassart *et al.* 2007).

This hypothesis has been recently supported by the description of the biochemical defect occurring in AM (Westermann *et al.* 2008). A multiple acetyl-CoA dehydrogenase deficiency (MADD) was found in confirmed cases of AM. Dehydrogenase enzymes catalyse key events in fatty acid metabolism. They catalyse oxidation-reduction reactions using a coenzyme derived from riboflavin (vitamin B2) thus suggesting that AM might result from a riboflavin deficiency or blockage. This MADD leads to dysfunction of the most efficient way for generating energy by the mitochondria, i.e. oxidative phosphorylation from lipid substrates, therefore resulting in severe rhabdomyolysis, especially in postural and respiratory muscles. Identification of this metabolic defect is of paramount importance since it will contribute to improve the medical management of AM and will guide the search for the aetiological agent towards toxins that reproduce the identified defect.

Clinical signs

Clinical studies (Whitwell *et al.* 1988; Brandt *et al.* 1997; Votion *et al.* 2007) report that affected horses show a sudden onset of severe general weakness and muscular stiffness and, often become recumbent within a few hours. They are

sometimes even found dead on pasture without premonitory signs. Some are reluctant to move, others are so weak that they have difficulty keeping their head up (G. van Galen, personal observation).

The affected horses show increased heart and respiratory rate, often hypothermia and congestive mucosae. Most cases keep a good appetite and continue to pass faeces, although some suffer from oesophageal obstruction (Hosie *et al.* 1986; Whitwell *et al.* 1988; Brandt *et al.* 1997; Votion *et al.* 2007).

Dysuria with a distended bladder at rectal examination is frequently encountered. A lot of horses demonstrate signs of colic probably due to this bladder distension (Hosie *et al.* 1986; Brandt *et al.* 1997; Votion *et al.* 2007), but rarely are intestinal causes for these colic signs found, such as those described in the case report of Sherlock and Mair (2008). The urine is dark-brown in the acute phase due to the presence of myoglobin in the urine (myoglobinuria) (Hosie *et al.* 1986; Votion *et al.* 2007).

Subclinical cases have also been described and can be horses that graze on the same pasture as a clinically affected horse. They are often recognised when blood analyses are performed on co-grazers of the affected horse. These subclinical cases have significant increase of serum activities of creatine kinase (CK) (Delguste *et al.* 2002; Votion *et al.* 2007). They can, however, evolve into clinical cases and so it is important to recognise and monitor them closely. It is thought that they are in balance with the causative agent, but a sudden imbalance may occur due to a trigger or a stress factor resulting in the clinical development of AM. These stress factors are suggested to be cold weather, exercise (Votion *et al.* 2003), transport (G. van Galen, personal observation), or anaesthesia as described in the case of Sherlock and Mair (2008) where overt signs of AM were observed after the recovery.

Diagnosis

The clinical diagnosis of AM can be made based on history, clinical signs, blood and urine analysis, muscle biopsy and finally on *post mortem* examination (Delguste *et al.* 2002; Cassart *et al.* 2007; Votion *et al.* 2007).

History is of major importance in the diagnosis. No cases have yet been described that have not been out on pasture, probably because the aetiological agent is only found at pasture. Sometimes AM can occur as an outbreak and it is known that pastures where the condition has occurred before remain at risk in following years (Votion *et al.* 2007). So knowledge of previous cases on the particular pasture may facilitate the diagnosis. Excluding other forms of rhabdomyolysis, such as exercise-induced myopathies, is paramount. However, as mentioned earlier, it is speculated that exercise as any other forms of stress can predispose for developing AM (Votion *et al.* 2003) most probably because the metabolic defect recently described (Westermann *et al.* 2008) induces a metabolic imbalance that precludes to any additional energetic demand.

The clinical signs are typical for any severe rhabdomyolysis, but not specific at all for AM. It is therefore difficult to make a

diagnosis just based on clinical signs. However, the frequently apparent absence of pain in AM is surprising with regard to the suffering that usually accompanies other forms of severe rhabdomyolysis, especially exercised-induced myopathies.

At blood analysis muscle enzymes are massively increased, confirming the severe rhabdomyolysis (Hosie *et al.* 1986; Whitwell *et al.* 1988; Brandt *et al.* 1997; Votion *et al.* 2007). If CK levels remain below 10,000 ui/l, diagnosis of AM is challenging since one should be aware that the first blood analysis does not always demonstrate the highest CK levels (G. van Galen, unpublished data). Often hyperglycaemia and hyperlipaemia are present and liver enzymes are increased (Hosie *et al.* 1986; Whitwell *et al.* 1988; Votion *et al.* 2007). Hypocalcaemia is almost always found, but no other important electrolyte derangements are reported consistently. The urine is coloured due to the myoglobinuria, and should be differentiated from haematuria or haemoglobinuria.

A definitive diagnosis of AM may be made based on histology of muscle samples taken by biopsy or *post mortem*. The characteristic profiles of organic acids, glycine conjugates, acylcarnitines in urine and acylcarnitines in plasma found in AM affected horses might also be helpful in the diagnosis of the condition (Westermann *et al.* 2008). Biopsy is best performed in living horses on postural muscles and in *post mortem* on the intercostal muscles (Cassart *et al.* 2006). At necropsy, discoloured muscles and myocardium, congestive lungs, petechiae and black-reddish gastroenteric contents may be seen (Cassart *et al.* 2006). However, necropsy may also be disappointing with no specific observation. The most specific microscopic feature of AM is the important lipid accumulations in *type I* muscle fibres that undergoes Zenker necrosis/degeneration (Cassart *et al.* 2006).

Differential diagnosis

Other severe myopathies described in the horse are sporadic or recurrent exercise-induced myopathies, glycogen branching enzyme deficiency (GBED) in the foal, white muscle disease or nutritional myodegeneration, Streptococcal myopathy and post anaesthetic myopathy. Besides other severe myopathies, AM can be confounded with endotoxaemia, colic, neurological disorders (e.g. tetanus, botulism, tick paralysis, rabies, meningitis, spinal cord disease, grass sickness), intoxications (e.g. ionophores, strychnine, carbamates, organophosphates, *Cassia occidentalis*, acorn, white snakeroot), haematuria or haemoglobinuria of any cause (e.g. cystitis, calculi, bladder tumours, exercise-induced haematuria, urethral defects, renal haemorrhage, systemic haemolysis), or even lameness (e.g. iliac thrombosis, laminitis, polyarthritis, arthritis). Worth mentioning in respect to the differential diagnosis of AM is the fact that horses can develop increased muscle enzyme activity due to prolonged recumbency as described in the clinical report of Sherlock and Mair (2008).

In horses with colic, muscle fasciculations are often noted secondary to pain and/or to hypocalcaemia. These fasciculations, together with the frequent occurrence of colic in horses and other clinical signs of colic (tachycardia,

tachypnoea, congestive mucosae, recumbency and pain) make colic a very important differential diagnosis of AM. As shown in the case report by Sherlock and Mair (2008), they may even occur together.

Treatment

Since the aetiology of AM is not known, therapy of AM affected horses is mostly symptomatic. Nevertheless, one of the existing hypotheses about the aetiology includes clostridial infections (Delguste *et al.* 2002; Gerber *et al.* 2006). Administration of metronidazole (15 mg/kg bwt q. 8 h *per os*) might therefore be hypothetically helpful. Administration of botulism type C and D antiserum has also been proposed (Gerber *et al.* 2006).

It is of great importance to administer i.v. balanced electrolyte solution to horses with an acute myopathy to avoid acute tubular necrosis due to myoglobinuria. Together with fluid therapy, electrolyte and acid-base balance should be maintained. Since AM cases seem prone to the development of hypocalcaemia, special attention should be carried out for calcium imbalances administering slow i.v. calcium borogluconate (100–300 ml calcium borogluconate 20% until correction). Moreover, outcome of colic horses has recently been reported to be favoured by correction of their hypocalcaemia (Delesalle *et al.* 2005).

Histology of affected horses (Cassart *et al.* 2006) and metabolic studies (Westermann *et al.* 2008) have shown defects in the mitochondrial lipid metabolism of the muscle cell, but not in carbohydrate metabolism. This corroborates with the presence of hyperglycaemia and hyperlipaemia in blood analysis of affected horses (Brandt *et al.* 1997; Votion *et al.* 2007). Thus carbohydrate metabolism should be enhanced by i.v. administration of 5% glucose (2 ml/kg bwt/h), or oral administration of glucose (0.5 g/kg bwt b.i.d.). Glucose also supports the affected hepatic metabolism, by decreasing the need for hepatic gluconeogenesis. Insulin (15–30 iu subcut.) and heparin (40–250 iu/kg bwt subcut. b.i.d.) can be administered to further control the hyperlipaemia and hyperglycaemia. Supplementing affected horses with chromium (5 mg s.i.d. *per os*) will improve their insulin sensitivity (Anderson 2008), and will probably enhance their intersarcoplasmatic glucose-uptake. Most horses keep a good appetite; some of them are even craving for food (Votion *et al.* 2007). Given that the suspected defect is in lipid and not carbohydrate metabolism (Cassart *et al.* 2006; Westermann *et al.* 2008), it is proposed that concentrates with a high quantity of carbohydrates might be beneficial. This increase in carbohydrate content is contradictory to nutritional advice for several other equine myopathies, proposing a decrease of carbohydrate content and an increase of lipid content. The MADD found in AM affected horses is possibly due to a riboflavin deficiency or blocking and thus a supplementation of affected horses with this vitamin B2 (via B-complex vitamin supplementation) might also be interesting (Westermann *et al.* 2008). Support for muscular function and repair should be offered to these

horses by vitamins and antioxidants, such as selenium, and vitamins C and E.

Many affected horses have difficulties urinating and should be relieved by regular or continuous bladder catheterisation. If an indwelling catheter being placed or repeated catheterisation is necessary, broad spectrum antibiotics should be administered to prevent cystitis (e.g. trimethoprim sulphamethoxazole 30 mg/kg bwt b.i.d. *per os*). In general, horses fully regain their capacity to urinate once the myoglobinuria has disappeared (G. van Galen, unpublished data).

Although not all horses seem to suffer intensively (Votion *et al.* 2007) analgesia can be provided if necessary by nonsteroidal anti-inflammatory drugs (NSAIDs), morphine or morphine-derivatives. It should be noted that NSAIDs are a cause of renal toxicity and, especially with the large amounts of myoglobin passing through the kidneys, caution is advised with their administration. It is of major importance during administration of NSAIDs to maintain hydration and monitor renal indices such as BUN, creatinine and urinalysis to determine if renal impairment has occurred.

Due to the progressively affected respiratory muscles a severe hypoxia can develop (Delguste *et al.* 2002; Votion *et al.* 2007), and respiratory support in the form of nasal oxygen can be considered. For foals artificial ventilation might even be necessary.

Dantrolene sodium (2–2.5 mg/kg bwt in saline by slow i.v. administration) is proposed for limiting rhabdomyolysis in other myopathies and its use has been reported in AM-affected horses (Finno *et al.* 2006). This drug limits the rate of calcium release from the sarcoplasmic reticulum.

Once a horse is recumbent, regular turnings, good thick and clean bedding, and stimulating the horse to remain in sternal instead of lateral recumbency can prevent further muscle and pulmonary compression as well as the development of important decubital ulcers. For further information regarding the management of recumbent horses see Nout and Reed (2005). Affected horses should be exposed to stress (for example exercise, transport) as little as possible, since it might aggravate their condition.

Prognosis

The prognosis for most AM cases is not favourable. Most horses die within 3 days (Votion *et al.* 2007), although some nonsurvivors remain alive for a longer period up to 10 days (van Galen *et al.* unpublished data). The mortality rate of AM is estimated at 85% (Votion *et al.* 2004, 2007), but the outbreak occurring in the autumn of 2006 was less devastating with a mortality rate of 65% (G. van Galen, unpublished data). Fewer horses were found dead without premonitory signs and fewer horses were recumbent. It is of great importance for equine practitioners to know that AM-affected horses have a chance to survive. Prognostic factors recognised in clinical studies are normal respiration with normal arterial partial pressures in O₂ (PaO₂) levels and the absence of permanent recumbence. Serum activities of CK have not shown to be of prognostic value (Votion *et al.* 2007).

The survivors of the autumn 2006 outbreak had an uneventful recovery and surprisingly only showed minimal muscle wastage (G. van Galen, unpublished data).

It is important to inform the owner of the risk that other horses may become affected, clinically or subclinically. If possible, horses on the same pasture as an affected horse should be removed from the pasture and preferably placed in a box. If not enough boxes are available, young horses should have priority since they seem to be more at risk for AM (Votion *et al.* 2007). Their CK activities should be checked for several days and they should be monitored closely for any announcing signs (mainly weakness and stiffness).

Prevention

A large epidemiological investigation on Belgian confirmed cases enabled the identification of AM-favouring factors (Votion *et al.* 2008). In order to prevent AM it may be recommended that anthelmintics be administered regularly, to vaccinate, and to provide supplementary feeding and a salt block all year round. The mechanical harrowing of pasture (i.e. the spreading of manures) also favours AM and this common practice should be discouraged.

During the at-risk seasons (i.e. autumn and spring), horses should have access only to furnished grassland. Particularly humid pastures, or those where a stream/river flows and with considerable dead leaf accumulation in autumn, should be assigned for summer grazing especially if this pasture has a history of previous death(s) of horses. Giving water from the distribution network has also found to be a protective measure against AM.

When clinical series of AM are declared in neighbouring regions or countries, it is advisable to remove young and old horses from pastures, and horses maintained at pasture should be supplemented with concentrates rich in carbohydrates. It is worth noting that supplementing hay on the ground in a humid environment increases the risk of AM. A weather-dependent stabling should be considered with horses returning to pasture when several days of heavy frost have been encountered (it is thought that frost destroys the causal agent).

Conclusions

By gathering information on cases over Europe and continuing research by the partners of the AMAG (Atypical Myopathy Alert Group) on different aspects on the condition, the knowledge about AM grows year by year. On behalf of the AMAG, we are very grateful for the information received from veterinary surgeons and owners of affected horses. On the website of the AMAG, reporting of cases will continue, and can be performed by veterinarians as well as owners.

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