



Review

Equine atypical myopathy: A review

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Abstract

Atypical myopathy (AM) is an acute rhabdomyolysis syndrome that occurs at irregular intervals in grazing equines. An increasing number of outbreaks have been reported in recent years, including some from countries where the disease has not previously been diagnosed. In this review, clinical and other details of outbreaks of AM are analysed to better define its epidemiological profile. Potential aetiologies are discussed, the short clinical course of AM is described and the main biochemical and pathological findings are considered. Recommendations for medical management are suggested, based on a review of clinical reports. Biochemical and histopathological findings have been integrated in order to characterise the physiopathology of AM. There is an ongoing requirement to record new cases of this syndrome, ideally through an epidemiological network.

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Atypical myopathy (AM), formerly known as atypical myoglobinuria, is a specific, acute rhabdomyolysis described in grazing horses and characterised clinically by weakness, stiffness, recumbency and a high mortality rate following severe degeneration of particular muscle groups. While the condition has probably been encountered since earliest times (Hutyra and Marek, 1926; Bowen and Craig, 1942; Irwin and Pulsford, 1951; Pope and Heslop, 1960; Carthé et al., 1976), outbreaks seem to have become more frequent in recent years.

In 1984, a group of clinicians, pathologists and biochemists investigating an outbreak of myopathy in grazing horses in Scotland (Linklater, 1984) defined AM as a specific disease (Anonymous, 1985). The first large European outbreak occurred in Germany (Brandt et al., 1997), where

111/115 AM-affected horses died. Further outbreaks were reported in Belgium in 2000 (Delguste et al., 2002), in Switzerland in 2001 (Gerber et al., 2006) and in France in 2002 (Puyalto-Moussu et al., 2004), and particularly large outbreaks were described in Belgium and France in 2002, 2004 (Votion et al., 2007b) and 2006 (D.-M. Votion et al., unpublished data).

AM has now been recognised in many European countries (van der Kolk, 2006; Palencia and Rivero, 2007), and in 1966 Titschler and Miles reported an outbreak of myoglobinuria in the United States of America (USA), the details of which were highly compatible with AM (Tritschler and Miles, 1966). More recently, a seasonal pasture myopathy similar in many features to AM has been described in Minnesota in the USA (Finno et al., 2006).

In this review, reports of historical outbreaks of AM are considered in light of current knowledge and the symptomatic treatment and management of the disease is summarised. Biochemical and histopathological findings have been integrated to provide insights into the pathogenesis of the condition.

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Clinical history and epidemiology

Outbreaks of AM typically occur in the autumn although sporadic cases may present in the spring and less frequently in winter (Votion et al., 2003, 2007b). To date, cases of AM have not been reported during the summer (Hosie et al., 1986; Whitwell et al., 1988; Palencia and Rivero, 2007; Votion et al., 2007b). Although the disease does not appear to be contagious, several horses within a group may be affected simultaneously as it is clear that particular pasture characteristics predispose to the condition (Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b).

Outbreaks are frequently linked with climatic conditions, such as lack of solar radiation, the absence of heavy frost, and an excess of rain or an increased relative humidity for several days. Storm-force winds are also thought to be a predisposing factor (Hosie et al., 1986; Harris and Whitwell, 1990). The seasonal pasture myopathy recently described in the USA has also been associated with rainfall or thunderstorms and an absence of severe frost (Finno et al., 2006).

Atypical myopathy affects horses at pasture and is often restricted to particular regions within a country (Whitwell et al., 1988; Brandt et al., 1997; Puyalto-Moussu et al., 2004; Votion et al., 2007a,b). Pasture-related factors associated with an increased risk of AM include the presence of wet areas, the adjacency of a river, an increased pasture gradient and the presence of dead leaves.

Young, unbroken equines are predominantly affected (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Palencia and Rivero, 2007; Votion et al., 2007b) but there does not seem to be a breed or sex predisposition. The higher prevalence of AM in females is accounted for by the predominance of mares and fillies kept at pasture (Votion et al., 2007a). Most cases of AM have been reported in animals not in training, that were grazing old, permanent, bare pastures and that were receiving supplementary hay (Hosie et al., 1986; Whitwell et al., 1988; Votion et al., 2007b). Affected horses are typically <3 years of age and are often reported to be in good body condition (Hosie et al., 1986; Brandt et al., 1997; Votion et al., 2007a). However, animals in normal to poor body condition are more at risk for AM than those with excess body-weight, a factor that correlates with a reduced risk of AM. Regular vaccination, anthelmintic treatments and exercise are also associated with a reduced risk of AM.

The identification of risk factors associated with pasture management has facilitated the design of preventive measures despite the fact that the primary cause(s) of AM remain(s) undetermined. Given that the spreading of horse manure is a recognised risk factor, the regular collection of faeces from pastures is advised, although this may not always be practical where animals are extensively grazed. The provision of salt blocks and potable water also reduces the risk of disease development, as does reducing the time horses spend at pasture during inclement weather (Votion et al., 2007b).

Aetiology

Putative causes of AM include chemical toxicosis, virus infection, nutritional deficiencies, ionophore toxicosis, exposure to plant, bacterial or fungal toxins, to herbicides or to nitrates in the drinking water (Whitwell et al., 1988; Brandt et al., 1997). Many of these possible causes (i.e. chemical, herbicides, nitrates and ionophore toxicoses) have not been substantiated by large, case-controlled studies (Votion et al., 2007a) and complementary examinations (Whitwell et al., 1988; Brandt et al., 1997).

In horses clinically affected with AM, serology failed to demonstrate evidence of equine influenza virus, rhinopneumonitis virus, rhinoviruses, adenoviruses (Whitwell et al., 1988), Borna disease virus or herpesvirus infection (Brandt et al., 1997). Nutritional myopathy and ionophore intoxication share many features with AM, including acute oxidative skeletal muscle and myocardial degeneration, myoglobinuria and elevated serum creatine kinase (CK) concentrations (Novilla, 1992; Harris, 1996). Furthermore, although reported cases of AM have adequate serum, kidney and/or liver concentrations of α -tocopherol, their selenium status has varied from normal to severely deficient (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; D.-M. Votion et al., unpublished data). However treatment of AM-affected horses with vitamin E and/or selenium is often ineffective (Hosie et al., 1986; Brandt et al., 1997; Delguste et al., 2002). Taken together, these findings may suggest that the antioxidant status of a horse influences its susceptibility to the (yet unknown) AM aetiological agent. Selenium and other antioxidants have been shown as preventative of mycotoxicoses (Atroshi et al., 2002) and it could be speculated that the provision of dietary supplements and access to salt blocks to animals reduces their risk of developing AM through enhancing their antioxidant status (Votion et al., 2007a).

There is no evidence that ionophore intoxication through the accidental ingestion of contaminated feed intended for other species or through the ingestion of naturally produced ionophores is involved in the pathogenesis of AM (Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b). Nevertheless, the involvement of a naturally produced (and so-far unidentified) ionophore, perhaps present in very low concentrations, remains a possibility (Novilla, 1992).

Although no pathogenic bacteria have been isolated from the tissues of AM-affected horses post-mortem (Hosie et al., 1986), recent studies have speculated that toxins produced by *Clostridium sordellii* and *bifermantans* may have a role in the pathogenesis of the condition (Gerber et al., 2006). No specific plants have been implicated in the aetiology of AM (Hosie et al., 1986; Robinson, 1991; Brandt et al., 1997; Puyalto-Moussu et al., 2004; Votion et al., 2007b). *Ranunculus repens* and *Acer pseudoplatanus* (a familiar tree in Belgium) were the only plants common to premises surveyed in Belgium (Votion et al., 2007b).

The accumulation of dead leaves on pasture and the increased humidity, factors associated with an increased risk of AM, also favour mould growth and mycotoxin production (Votion et al., 2007a). *Trichoderma*, *Alternaria*, *Cladosporium*, *Aspergillus* and *Penicillium* spp., some of which are known to produce mycotoxins, have been isolated from grass, hay wood or feed samples from some affected premises (Anonymous, 1985; Whitwell et al., 1988; Brandt et al., 1997).

Clinical signs

AM usually starts abruptly with the sudden onset of pronounced muscular weakness and stiffness (Anonymous, 1985; Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b). Rare premonitory signs include depression, colic, anorexia, signs similar to those observed with oesophageal obstruction and stiffness of the hindlimbs (Brandt et al., 1997; Votion et al., 2007b). Within hours, AM-affected horses are unable to stand and animals are often found in lateral recumbency at pasture. Mortalities can occur within 72 h of the onset of signs (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b) and the mortality rate is estimated at 85% (Puyalto-Moussu et al., 2004; Votion et al., 2004).

Many of the clinical signs of AM are the consequence of postural and respiratory muscle degeneration. In rare instances, horses remain standing with a ventroflexed head, sometimes accompanied by subcutaneous oedema of the head and neck (Votion et al., 2007b). Affected animals remain quiet and conscious (Harris and Whitwell, 1990; Votion et al., 2007b) and those horses that are able to rise are usually unable to stand for more than a few minutes. On moving, stiffness is apparent and sweating and trembling are frequently observed. In a small number of cases there has been evidence of severe pain and of paddling movements of the limbs (Brandt et al., 1997). On deep palpation, affected muscles do not feel particularly firm and painful reactions are seldom elicited. Appetite may remain normal, or may be increased, and in some instances dysphagia has been reported (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Palencia and Rivero, 2007; Votion et al., 2007b).

Affected horses are usually afebrile or severely hypothermic (i.e. rectal temperature <36.5 °C) at the onset of clinical signs (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b). The hypothermia resolves when the horse is stabilised (Votion et al., 2007b). However the presence of hyperthermia does not preclude a diagnosis of AM. Heart rate is normal or moderately accelerated (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b) and although abnormal heart sounds (i.e. intermittent cardiac irregularity or murmurs) have been infrequently reported, there are no specific electrocardiographic or echocardiographic abnormalities associated with AM (D.-M. Votion et al., unpublished data). The rapid onset of laboured breathing is associated with

a poor prognosis. (Votion et al., 2007b). Conjunctival mucous membranes may initially be normal in colour but marked reddening develops with time (Brandt et al., 1997; Votion et al., 2007b).

On rectal palpation the bladder may feel significantly distended. This distension may contribute to the signs of colic observed as these signs ameliorate when the bladder empties (Hosie et al., 1986; Brandt et al., 1997; Votion et al., 2007b). The urine is dark-brown in colour except in a few animals that have died acutely, or where the condition has been present for several days by which time severe rhabdomyolysis has presumably ceased (Hosie et al., 1986; Harris and Whitwell, 1990; Votion et al., 2007b).

Laboratory findings

Plasma CK concentrations are the most specific biochemical indicator of AM, rising rapidly in association with the onset of clinical signs to >10,000 IU/L and often reaching >100,000 IU/L (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Palencia and Rivero, 2007; Votion et al., 2007b). However, CK concentration is not a useful as a prognostic indicator, a better approach being the measurement of the arterial blood oxygen tension (Pa_{O₂}) as decreased Pa_{O₂} is associated with deterioration of clinical signs and death (Votion et al., 2007b).

Electrolyte imbalances, such as those found in exercise-induced rhabdomyolysis (i.e. hyponatraemia, hyperchloraemia and hypokalaemia), are rarely found in cases of AM (Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b). Blood urea and creatinine values are frequently within normal ranges indicating adequate renal function (Brandt et al., 1997; Votion et al., 2007b). Hypocalcaemia and hyperglycaemia are almost constant features of the condition (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b) and high serum triglycerides are also frequently found (Votion et al., 2007b). Other common biochemical findings include the detection of markers of myocardial damage such as the troponin, increased liver enzyme levels and elevated total white cell counts usually due to neutrophilia (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Votion et al., 2007b).

Treatment

Horses affected by AM require intensive supportive and nursing care, which is often difficult to administer under field conditions, particularly in the inclement weather often associated with disease outbreaks. Whenever possible, affected horses should be carefully transported to a deeply bedded stable, which facilitates warming of hypothermic animals and therapeutic intervention.

Symptomatic treatment includes intensive fluid therapy, multivitamin injections and, if necessary, analgesia. Intravenous fluid therapy along with treatment with selenium

and vitamin E did not prevent deaths from AM (Hosie et al., 1986; Brandt et al., 1997). However, aggressive treatment with antioxidants, anti-inflammatories and fluids may be beneficial at least to decrease the potential sequels, the pain and hopefully to increase the chance to survive (Finno et al., 2006). Supportive therapy should also include the restoration of calcium homeostasis and the regular emptying of the affected animal's bladder.

Given that AM is associated with dysfunction of lipid rather than of carbohydrate metabolism (Votion et al., 2007b), it is hypothesised that carbohydrate administration favours the survival of AM-affected animals by providing essential supportive nutrition. However such an approach requires monitoring of blood glucose levels and possibly insulin administration to counteract the hyperglycaemia frequently found in AM-affected horses. Oral dosing is the preferred route of carbohydrate administration and a stomach tube may be required for animals that have difficulty swallowing.

Severe respiratory dyspnoea is associated with a poor prognosis and euthanasia should be considered if this clinical feature is observed. During the clinical course of AM, PaO₂ levels indicate that increasing dyspnoea (most probably from respiratory muscle degeneration) correlates with increasing hypoxia (Votion et al., 2007b). If appropriate laboratory facilities are available, the regular assessment of PaO₂ is advised as this provides a useful prognostic indicator. As long as the PaO₂ value is >85 mmHg and no severe pain is present, treatment should continue and oxygen administration may be attempted to maintain this parameter. From our limited experience of horses that survive, those that do recover do so quickly (D.-M. Votion et al., unpublished data).

Measurement of CK levels in the cohorts of AM-affected horses can identify subclinically affected animals (Votion et al., 2007b), the early recognition of which is useful in preventing clinical disease through intervention with intensive therapy as outlined above. When AM is suspected, co-pastured horses should be housed or, at the very least, removed from the 'affected' pasture.

Necropsy and histopathological findings

At necropsy, pale regions in the postural and respiratory muscles, particularly intercostals, diaphragm and muscles of the neck and shoulder have been consistently found (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Cassart et al., 2007). Pale areas may also be observed in the myocardium. However in some cases, lesions are not observed in either the skeletal or cardiac muscles.

There are consistent histopathological reports of myodegeneration of the diaphragm and intercostal muscles, features that probably account for the high mortality associated with AM (Cassart et al., 2007). Other severely affected muscles include those of the neck and shoulder, the biceps, the masseters and, to a lesser extent, the muscles of the back and hindquarters. Within an affected muscle, the degree of myodegeneration may vary greatly, with

some myofibres exhibiting fragmentation and swelling while adjacent fibres are normal (Hosie et al., 1986; Whitwell et al., 1988; Brandt et al., 1997; Cassart et al., 2007; Palencia and Rivero, 2007). The myodegeneration is morphologically consistent with Zenker's degeneration, is multifocal and monophasic and typically (but not exclusively) affects oxidative rather than glycolytic fibres (Brandt et al., 1997; Cassart et al., 2007; Palencia and Rivero, 2007). Retraction bands can be observed within sarcolemmal sheaths which usually remain intact (Whitwell et al., 1988; Cassart et al., 2007; Palencia and Rivero, 2007). Myofibre nuclei appear normal and are peripherally located within the cells (Whitwell et al., 1988; Cassart et al., 2007). Although a small proportion of degenerate fibres are infiltrated by macrophages and/or neutrophils, overall, the inflammatory response is minimal (Whitwell et al., 1988; Cassart et al., 2007).

Histochemical 'Oil red O' staining of frozen muscle samples has indicated marked accumulation of neutral fat within myofibres (Brandt et al., 1997; Cassart et al., 2007; Palencia and Rivero, 2007) and staining for nicotinamide adenine dinucleotide (NADH) reductase and succinate dehydrogenase (SDH) in myofibres indicates that these cells have an overall weak oxidative potential (Cassart et al., 2007; Palencia and Rivero, 2007). Periodic acid-Schiff staining has failed to demonstrate either increased cytoplasmic glycogen or polysaccharide (Cassart et al., 2007; Palencia and Rivero, 2007) and alizarin-red staining does not indicate calcium salt deposition (Cassart et al., 2007).

Histopathological changes in the myocardium have been inconsistently reported as mild to severe myocardial degeneration with lipid accumulation (Whitwell et al., 1988; Brandt et al., 1997; Cassart et al., 2007). Myocardial mineralisation has not been described and no abnormalities have been seen in the conducting fibres (Whitwell et al., 1988; Cassart et al., 2007). In 32 cases examined by Cassart et al. (2007), no significant microscopic findings were found in the liver, pancreas, urinary bladder, brain, spinal cord or parasympathetic ganglia.

Pathophysiology

Atypical myopathy exhibits morphological and biochemical changes consistent with a primary myopathy, not dissimilar to those of toxic or nutritional origin (Goed-gebuure, 1987; Cassart et al., 2007). Phytotoxins (e.g. tremetone from white snakeroot plants) and ionophores induce rhabdomyolysis in horses and nutritional myopathy in this species shares many clinical and pathological features with AM (Votion et al., 2004). These similarities may reflect the fact that these myopathies, of varying aetiology, share a common final pathway of myodegeneration. If this is the case, evidence linking specific factor(s) with AM will require careful investigation of the early, potentially more unique stages, of its pathogenesis.

Histochemical staining of AM-affected muscle for adenosine triphosphatase (ATPase) suggests that the degenerative

process selectively targets type I rather than type II fibres (Brandt et al., 1997) and increased lipid is also noted in type I fibres (Cassart et al., 2007; Palencia and Rivero, 2007). These findings, taken together with evidence that affected myofibres have weak oxidative potential and ultrastructural evidence of mitochondrial injury suggest a role for mitochondria in the pathogenesis of AM. Further investigations will require assessment of the activity of other enzymes to elucidate more precisely those alterations in myofibre oxidative processes (Votion et al., 2007c; Westermann et al., 2007a).

Recently, defects in lipid metabolism have been incriminated in the pathogenesis of non-exertional rhabdomyolysis (Westermann et al., 2007b), a metabolic myopathy resulting from multiple defects in the activity of β -oxidation enzymes. Similarly, multiple acyl-CoA dehydrogenase deficiency (MADD) results from defects in several mitochondrial dehydrogenases that use flavin adenine dinucleotide (FAD) as a co-factor. Diagnosis of MADD in horses is based on the finding of characteristic profiles of organic acids and acylcarnitines in urine and plasma. The two reported cases of equine MAAD exhibit hyperglycaemia similar to AM, a feature not reported in human patients (Darras and Friedman, 2000). Although MADD in humans is considered a genetic disorder, the cause of MADD in horses remains unidentified. The question as to whether a toxin might mimic this dysfunction of fatty acid oxidation must also be considered in AM.

Conclusions

Determining the true incidence of AM and its associated risk factors, and defining a specific aetiology are difficult given the unpredictability of outbreaks and the short clinical course of the disease. Increased awareness of the condition will assist future investigations by highlighting the need for early and ongoing sampling of clinical cases and by enhancing our knowledge of its epidemiology. It is vital to record the occurrence of cases of AM through an established epidemiological network. Regional differences in AM-associated indicators or risk factors are likely to exist given differences in pasture characteristics and horse management and comparative analysis of such data may identify common factors. This, in turn, is likely to enhance our knowledge of risk factors and pinpoint potential aetiological agents.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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¹ See: www.myopathieatypique.be.

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