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History and Clinical Features of Atypical Myopathy in Horses in Belgium (2000–2005)

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Background: The emergent nature of atypical myopathy or atypical myoglobinuria (AM) necessitates precise description of its clinical and epidemiologic features.

Purpose: To define key features of AM to help practitioners recognize the disease and to advise owners to take preventive measures.

Animals: Belgian cases of AM confirmed by histology (CC horses; n = 57) from autumn 2000 to spring 2005 were included in the study. Co-grazing horses (Co-G horses; n = 77) that remained free of any abnormal clinical signs constituted a control group.

Methods: History, environmental characteristics, clinical signs, and laboratory results associated with AM were determined by a retrospective case series study.

Results: Young horses in poor or normal body condition were found to be at risk for AM. Pastures were characterized by poor natural drainage and vegetation of low nutritional value. Features of AM were seasonal occurrence, apparent link with weather conditions (ie, lack of solar radiation with no heavy frost and an excess of precipitation or relative humidity), sudden onset of clinical signs, and rapid death. Evaluation of serum creatine kinase activity indicated severe muscle destruction in CC horses and subclinical disease in a few Co-G horses.

Conclusions: The association of AM with specific environmental conditions and individual animals suggests that young horses should not be pastured on bare premises subject to humidity when the weather has been very wet and cold for several days. Management of AM outbreaks should include control of Co-G horses who are apparently healthy.

Key words: Clinical signs; Epidemiology; Laboratory findings; Pastures.

Since the middle of the 20th century, there have been sporadic reports of frequently fatal acute rhabdomyolysis affecting grazing horses in various parts of the world.[1–6] This syndrome, recognized as a specific myopathic disorder of horses in 1984,[7] was named atypical myoglobinuria. The recognition of this pathologic entity, also known as atypical myopathy (AM),[8] followed the occurrence of series of cases in various parts of Scotland.[6,9] Since that time, AM has been reported periodically in the United Kingdom.[10–13] In the fall of 1995, more than 100 horses died from the condition in Northern Germany,[14] and more recently, AM has been identified for the first time in Belgium[15] and France.[16] Lately, a review of cases of nonexertional rhabdomyolysis, which was previously attributed to tremetone toxicosis resulting from ingestion of white snakeroot plants, suggests that a seasonal myopathy similar to AM may also be present in the United States.[17] Indeed, tremetone was not detected in any of the samples collected from the reviewed cases, whereas the clinical, postmortem, and histologic findings in these horses were similar to those observed in AM, including the specific groups of muscles affected[6,10,14,15,18,19] and the marked accumulation of lipid in myofibers.[18]

Until now, the etiology of AM has remained unidentified. Because of the emergent nature of AM, a precise description of its clinical and epidemiologic features is essential to help practitioners recognize suspected cases. Several single episodes of AM have been reported in the literature,[6,9–16] but large-scale studies are lacking. For that purpose, the data were collected from all Belgian cases of AM confirmed by histology since the first recognized Belgian outbreak in November 2000[15] until the end of the spring 2005. By compiling these data, the aim was to define converging elements in the history, clinical signs, and biochemical changes associated with AM.

Materials and Methods

Selection of Cases

Between November 2000 and May 2005, 196 Belgian horses with history and clinical signs suggestive of AM were reported to the 2 Belgian veterinary schools (Liège University and Ghent University). Only horses in which AM was confirmed by muscle histology (CC horses) were considered. Diagnosis of AM was confirmed when histologic analysis of postmortem samples in-

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dicated a multifocal process compatible with Zenker degeneration and necrosis in fibers of postural (eg, subscapularis) muscles, respiratory (eg, intercostals) muscles, or both.[18] These groups of muscles were chosen because postural and respiratory muscles have been found to be the muscular groups mainly involved in AM.[6,10,14,15,18,19] Several CC horses were co-grazing with apparently healthy horses. These pasture companions that remained free of any abnormal clinical signs constituted the group of co-grazing horses (Co-G group). The Co-G group was used to determine risk factors associated with demographic data and to define specific laboratory findings associated with clinical signs of AM.

Collection of Data

History. Using a written questionnaire, owners of the horses included in this study were asked to provide data on the CC horses and their Co-G counterparts. Questions included information about individual horses and pasturing and feeding practices. The date at which the first signs of AM were seen in CC horses and the presenting complaints were also requested.[20] In addition, it was asked whether animals other than horses (domesticated or wild, including birds) were found dead on the pasture in the weeks preceding or following the occurrence of AM in CC horses. The body condition of horses was assessed by the owner as follows: thin, normal weight, and overweight.

Environmental Factors. Horse owners were also asked to provide information about the pastures where the animals were grazing when they presented with signs of AM.[20] The geographic distribution of the premises was determined with the use of a global positioning system (GPS[a]). This enabled the study of soil and climatic data by combining existing data sets. The natural drainage and hydromorphic characteristics of the soils of the pastures were studied by using a numeric version of the soil map of Belgium. This is a detailed map (scale, 1:20000) of the Walloon region where more than 90% of CC horses were recorded. Based on morphologic features, this map distinguishes the various types of soils.[21] The natural drainage and hydromorphic characteristics of the concerned soils were analyzed according to texture, hydromorphology, diagnostic horizon, and, if relevant, stoniness. Using the criterion ''diagnostic horizon,'' valleys and depressions were highlighted as such geomorphologic layouts may also influence hydromorphology.

For 31 outbreaks, topographic meteorologic data were collected from the nearest representative meteorologic stations (National Meteorological Institute network) a few days before and at the date of the onset of AM. Relevant data were collected for daily rainfall, minimum and maximum temperature, mean relative humidity, sunshine duration, maximum wind speed, and average atmospheric pressure.

An accurate inventory of the floristic composition of the herbaceous cover was determined in 9 premises where AM broke out. The premises were selected to represent the different natural sites found in Wallonia, where the CC horses were located. The Braun-Blanquet method[22] was used to estimate the coverage of each species. Herbaceous species that were outside the pasture but nonetheless accessible to the grazing horses were noted. A list of shrubs and trees within or surrounding the premises was also established.

Clinical Signs. Data on clinical signs were obtained from medical records[20] and from interviews with the referring veterinarians. The date and hour at which any abnormal clinical sign was first observed was considered as the onset of the illness. Whenever possible, clinical examination of the Co-G horses was performed to ensure they were clinically healthy.

Laboratory Tests

Whole blood was collected by jugular venipuncture, and serum was stored at $-80^{\circ}C$ until analysis. Serum activities of creatine kinase (CK), aspartate aminotransferase (AST), total lactate dehydrogenase (LDH_{Tot}) and its isoforms (Iso-LDH_{1-5}), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), and sorbitol dehydrogenase as well as conjugated and total bilirubin ($bilirubin_{Conj}$ and $bilirubin_{Tot}$, respectively), urea, creatinine, total and ionized calcium (Ca_{Tot} and Ca^{2+}, respectively), electrolytes, total protein, haptoglobin, troponin I (a protein specific for the myocardium), myoglobin, triglycerides, glucose and lactate were determined by standard laboratory methods. Hematologic testing included coagulation times, complete blood count, hemacrit, arterial partial pressures in O_2 and CO_2 (Pao_2 and $Paco_2$, respectively), and acid-base status in arterial and venous blood (pH and base excess). In some cases, blood sampling was repeated over time. Whenever achievable, the Co-G horses were sampled as soon as possible after the onset of AM in CC horses. Enzyme activities (CK, AST, LDH_{Tot} and Iso-LDH_{1-5}, ALP, GGT, and sorbitol dehydrogenase), $Bilirubin_{Conj}$ and $Bilirubin_{Tot}$, Ca_{Tot} and Ca^{2+}, haptoglobin, troponin I, triglycerides, and glucose were measured, and complete blood count was performed, as these parameters were found to be the most frequently modified in the CC horses.

Statistical Analysis

The mean of the quantitative parameters in each group with unequal variance was compared using Welch's test.[23] Risk factors calculated for different parameters were evaluated by mean of odds ratios as defined by Grenier,[24] which aimed to compare the odds of exposure among CC horses with the odds of exposure among Co-G horses. The limit of statistical significance of the conducted tests was defined as $P \leq .05$.

Results

From the 196 suspected cases, AM was confirmed by histologic testing in 57 horses, which were thereafter included in the study. In the remaining horses, AM was eliminated or remained unconfirmed, either because histologic examination was not performed or because the animal survived. The CC horses originated from 42 different premises. They were co-grazing with 78 pasture companions, of which 77 did not exhibit any clinical signs, therefore meeting the selection criteria described for the Co-G group.

History

Individual Horses. The age of the CC horses ranged from 4 months to 11 years (mean ± SD, 2.8 ± 2.6 years; median, 2.0 years; mode, 18 months). Within the CC horses, there were no suckling foals drinking exclusively dam's milk. More than 82% of the CC horses were younger than 4 years vs 54% of the Co-G horses (mean ± SD, 5.8 ± 5.9 years; median, 3.5 years; mode, 24 months). A significant difference was found for mean age between the CC and Co-G groups (Welch's test; $df = 88$; $P = .0002$). Within the CC and Co-G groups, the oldest horses were 11 and 25 years old, respectively.

Demographic data and associated risk factors for AM are shown in Table 1. AM occurred in at least 14 breeds within, by order of frequency, saddle horses, ponies, and draught horses. No donkey was diagnosed

Table 1. Demographic data and associated risk factors for atypical myopathy.[a]

	CC		Co-G				
	n	N	n	N	Odds Ratio	95% Confidence Interval	
Type							
Saddle horses	30	57	39	71	0.91	(0.45–1.82)	NS
Ponies	23	57	20	71	1.71	(0.82–3.56)	NS
Draught horses	4	57	8	71	0.62	(0.18–2.08)	NS
Donkeys	0	57	4	71	0.13	(0.00–2.47)	NS
Sex							
Females	42	56	35	55	1.69	(0.75–3.79)	NS
Colts and stallions	12	56	12	55	0.97	(0.40–2.37)	NS
Geldings	2	56	8	55	0.25	(0.05–1.10)	NS
Colts, stallions, and geldings	14	56	20	55	0.59	(0.26–1.32)	NS
Body condition							
Thin	4	43	0	55	3.08	(1.01–9.39)	+
Normal weight	35	43	41	55	2.20	(1.01–4.79)	+
Overweight	4	43	14	55	0.25	(0.09–0.69)	−
Previous illness	2	30	2	50	1.70	(0.28–10.43)	NS

CC, cases of atypical myopathy confirmed by histology; Co-G, clinically healthy co-grazing equidaes; N, number of total response for each category; n, number of positive response for each category; NS, not significant; (+), risk factor, (−), protection factor, both statistically significant at $P = .05$.

[a] Risk factors are presented as odds ratios (and 95% confidence interval).

with the condition. A large percentage of affected horses were females. Within the CC group, 4 horses were thin, and the majority of the others were in good body condition. Horses in poor or normal body condition were found to be more at risk for AM than overweight horses. Previous illnesses reported in the history were dermatologic (n = 1) and respiratory (n = 1) problems in CC horses and dermatologic conditions (n = 2) in Co-G horses. One CC horse had shown signs of AM 2 years before its death. Its first episode of myopathy occurred simultaneously with an AM outbreak that had been fatal to its 2 pasture companions (both were included in the CC group in our study).

Pasturing. Pasturing history was well-defined for 48 of the 57 CC horses. All CC horses were affected while at grass, except for 1 horse that had been stabled for a day after onset of AM in a pasture companion. All had been grazing the premise for at least 1 week when the disorder occurred, except for 1 horse that had been changed from its regular pasture the day before the onset of clinical signs. Fifty-five percent of CC horses had been grazing the premise for more than 3 months when affected by AM. Only 1 horse in the CC group was regularly stabled overnight; all others were at pasture full-time.

The mean (± SD) number of horses at pasture was 3.5 ± 1.9 when the disease broke out; 1.4 ± 0.7 horses (mean ± SD) were affected by AM (mean ± SD disease rate within pastures: 44 ± 21%). AM occurred repeatedly on 2 premises over the 2000–2005 observation period.

Feeding Practices. Fifty-two percent of horses in the CC group received additional feeding at the time of the onset of AM. From these supplemented horses, 65% received hay and 30% received a complete mix. Apart from 1 horse, none of the horses received both hay and concentrates simultaneously. None had access to feed intended for another species or may have been accidentally exposed to ruminant or poultry feed additives (ie, there was no exposure to ionophore-containing feedstuffs).

Seasonality. During the period considered, confirmed cases of AM occurred more frequently in autumn (86%). Some cases (14%) were recorded during spring and no CC horses were encountered during winter or summer. Outbreaks of AM occurred from mid-October (15th) to mid-December (17th) during autumn and from the beginning of April (7th) to the end of May (20th) during spring. Thus, AM showed a seasonal occurrence: more than 90% of cases occurred within a 5-week period.

Presenting complaints. Horses were acutely affected by AM, usually without prodromes (81%). When present, initial signs included diminished appetite (n = 4), decreased mental status (n = 3), signs of colic (n = 2), anorexia (n = 1), forelimb lameness (n=1), stiffness of the hind limbs (n = 1), and esophageal obstruction (n = 1).

Miscellaneous. No other species suffered mortality associated with the clinical outbreaks of AM in horses.

Environmental Factors

Overview of the Pastures. The owners of the horses usually described the grazed pastures as particularly bare, containing humid areas, crossed by or being bordered by a watercourse and sloping. The presence of trees and shrubs around or within the premises was almost always reported (Table 2).

Table 2. Characteristics of the pastures (42 locations).

Parameters	Relative Frequency (%)	No. of Answers
Grassland		
Sparse	84	29/42
Lush	16	29/42
Features of the pastures		
Sloping pasture	79	34/42
Surrounded by or containing trees	97	35/42
Humid pasture	58	36/42
Surrounded by or containing a watercourse	48	27/42

Drainage Characteristics of the Pastures. From the 42 premises where AM was confirmed, 31 were accurately located using the GPS. Study of the soil confirmed that most pastures (70%) were humid areas or had pedologic characteristics that favored humidity (eg, valley or depression) or were directly contiguous to areas with such features.

Weather Conditions. Climatic data were compiled for the 31 premises located by GPS. It was shown that during the autumn of 2001 and 2005, no CC horses were observed and only 2 CC horses were observed during autumn 2003. Monthly October sunshine durations of these 3 autumnal seasons were relatively longer than those of October 2000, 2002, and 2004. For example, at the Saint-Hubert meteorologic station (altitude 558 m), which is situated in the area of concern, monthly October sunshine durations were 59 hours 30 minutes, 70 hours 50 minutes, 32 hours 59 minutes for the years 2000 (11 CC horses), 2002 (20 CC horses), and 2004 (16 CC horses), respectively, whereas monthly October sunshine durations were 100 hours 05 minutes, 104 hours 55 minutes, and 156 hours 55 minutes for the years 2001 (2 CC), 2003 (5 CC), and 2005 (3 CC), respectively. Normal October sunshine duration for this station is 108 hours 30 minutes.

During the periods covered by the study, 2 events of very strong wind were observed with 108 km/h and 112 km/h maximal wind speeds recorded at Saint-Hubert meteorologic station, respectively. These events were followed by a series of 6 CC outbreaks and a series of 14 CC outbreaks, 5 days and 1 day, respectively after these windy days.

Synoptic meteorologic evaluation of the days of AM outbreaks indicated that a regional west wind and an oceanic air mass advection were present on 29 of the 31 premises studied (93%). Cases of AM were recorded more frequently (12 versus 4 outbreaks on 31 premises) when strong cyclonic conditions (ie, average daily atmospheric pressure $<$1005 hPa) were observed rather than strong anticyclonic conditions (ie, average daily atmospheric pressure $>$1025 hPa). Only 2 outbreaks of the 31 studied were observed on days with minimum daily air temperature $<0^{\circ}$C. Most outbreaks (78%) were observed on days with minimum daily air temperature between 0°C and 8°C, and 80% of these days had daily average relative humidity $>$90%. The 10 days preceding the outbreaks were usually characterized by a lack of solar radiation ($<$ 1 hours 30 minutes of sunshine) but no frost and an excess of precipitation or relative humidity.

Trees, Shrubs, and Ground Cover. The complete list of vegetation is available on request. The general aspect of the visited premises of CC reflected overgrazing: the vegetation was deteriorated because of trampling, and in some areas the ground was bare and organic matter had accumulated. In particularly bare areas, *Trifolium repens,* which sustains trampling was the most frequently found leguminous vegetation. In areas where feces were amassed, nitrophilous plants were found.

Several plants and trees that were found where CC horses were located are known to be toxic for livestock or horses.[25] Among plants toxic for horses, *Digitalis purpurea*, *Glechoma hederacea*, *Hypochoeris radicata*, *Pteridium aquilinum*, *Senecio jacobaea*, *Solanum nigrum*, *Ranunculus acris*, *Ranunculus repens*, *Trifolium* spp, and *Vicia sepium* were found. Leaves and branches of numerous shrubs and trees were accessible to horses, especially in autumn. *Acer pseudoplatanus* was present in all pastures CC horses visited. From trees known to be potentially toxic for horses, *Quercus robur* was found in 5 of the 9 affected locations.

Clinical Signs

Complete clinical records were available from 30/57 AM-affected horses. Gaps in medical records were attributable to limited investigations performed by the veterinarians, absence of annotation of the observations, or because the horse died before the veterinarian had time to perform a clinical examination.

Clinical Course of the Condition. All of the CC horses died within 3 days after the onset of clinical signs of AM (mean $\pm$ SD, 26.3 $\pm$ 16.9 hours; range, 3–72 hours). Fifty-one percent died spontaneously, and 49% were euthanized. Three CC horses were found dead at pasture. Only 2 CC horses were exercised in the hours preceding the onset of clinical signs (ie, a walking ride and a weaning the day before onset of AM).

Clinical Signs. Clinical signs present in CC horses are shown in Table 3. Weakness, recumbency (all horses in sternal recumbency finally adopted lateral recumbency), myoglobinuria (observed during spontaneous urination or after urine collection), stiffness, depression, muscle tremors, respiratory difficulties, sweating (localized or generalized), and signs of colic were the most frequently observed clinical signs. Dysphagia occurred in several horses, but the CC horses rarely were anorexic. Other common signs included difficulty standing and reluctance to move.

Results of the clinical examination of CC horses are reported in Tables 4 and 5. Clinical examination revealed that CC horses were frequently severely

Table 3. Frequency distribution of clinical signs in horses confirmed for atypical myopathy by histologic testing (by order of frequency).

Clinical signs	Relative frequency (%)	No. of answers
Signs with an incidence >50%		
Weakness	100	28/57
Recumbency	96	47/57
- Sternal	29	41/57
- Lateral	71	47/57
Myoglobinuria	95	39/57
Full bladder on palpation	80	15/57
Stiffness	80	30/57
Depression	72	29/57
Trembling	71	31/57
Able to get up	70	40/57
- Difficulty getting up	92	24/57
- Difficulty standing up	73	26/57
- Refusal to move	66	32/57
Sweating	57	30/57
Signs with an incidence of <50%		
Signs of colic	42	31/57
Paddling	33	24/57
Hemorrhagic diathesis	32	22/57
Dysphagia	31	29/57
Anorexia	18	33/57
Edema at the level of the head	15	13/57
Absence of consciousness	7	15/57

hypothermic and rarely hyperthermic. Diseased horses most often had tachycardia. Occasionally, cardiac arrhythmias or heart murmurs were found. Respiratory difficulties (ie, tachypnea and expiratory dyspnea) progressed with time and frequently were the main reason for euthanasia. Mucosa were frequently congested, and capillary refill time was increased; 2 horses showed signs of icterus 2 days after the onset of clinical signs. When palpated, the urinary bladder frequently was distended.

Laboratory Findings

Laboratory findings in CC horses are expressed as mean ± SD in Table 6. Table 7 shows results that were significantly different between the CC and Co-G groups. All other parameters showed either minor or no difference or excessive variability (ie, from normal to abnormal value in CC horses) to be considered of clinical relevance to the diagnosis of AM. When a parameter was followed over time, only the earliest result was used for statistical analysis.

In all CC horses, muscle enzyme activity was severely increased. In this group, hypocalcemia, high haptoglobin concentration, hyperglycemia, hyperlipemia, and increased liver enzyme activity were frequent but were not constant findings. Troponin I was always detected in high amounts in the serum of AM-affected horses. Except for AST enzyme activity, a statistically significant difference was found when CC horses were compared with Co-G horses for all of the aforementioned parameters. Despite extensive muscular damage, changes in serum electrolyte concentration were not always found. Hematologic alterations were not consistently present, but when observed, neutrophilia was most frequently identified. The Co-G horses were sampled within 1.5 ± 1.6 days after the onset of clinical signs in their CC pasture companions. Some individual horses in the Co-G group had results outside the normal range for CK, AST, LDH_{Tot} and ALP activities, Ca_{Tot}, Ca^{2+}, haptoglobin, troponin I, and glucose. Five of the 38 Co-G horses for which CK was measured had enzyme activity >2000 U/L. When followed over time, arterial blood gases showed a progressive deterioration of gas exchanges in CC horses (decreased Pao_2 and $Paco_2$), which was associated with an increase in dyspnea.

Discussion

The diagnosis of AM was made based on the observation of severe fiber degeneration in postural and respiratory muscle according to Cassart et al.[18] The histologic technique used may not have allowed microscopic lesions of AM to be differentiated from those induced by several other causes of rhabdomyolysis (eg, exercise-induced rhabdomyolysis, nutritional myopathy). Based on history and individual characteristics, these conditions were considered to be unlikely in CC horses. Only 2 CC horses had performed physical activity a few hours before showing signs of rhabdomyolysis. Previous exercise was not considered as a criterion for exclusion. The muscles primarily involved in AM are rich in type I fibers,[6] as opposed to exercise-induced rhabdomyolysis in which degeneration affects primarily type II fibers of the muscles of locomotion.[26]

To avoid bias because of case misclassification, the information presented here concerns exclusively cases of AM confirmed by histology rather than suspected cases based on clinical signs alone. Consequently, only fatal

Table 4. Results of the clinical examination of horses confirmed for atypical myopathy by histology (quantitative parameters).

Parameters	Mean (SD)	Range	No. of Answers	Normal Values
Rectal temperature (°C)	36.8 (1.4)	(33.6–40.0)	33/57	37–38.5
Respiratory rate (breaths/min^{-1})	32.9 (18.2)	(12.0–88.0)	23/57	<15
Heart rate (beats/min^{-1})	66.4 (22.5)	(32–130)	30/57	<45
Capillary refill time (seconds)	2.9 (0.8)	(2–5)	23/57	2 seconds

Table 5. Results of the clinical examination of horses confirmed for atypical myopathy by histology (qualitative parameters).

Parameters	Relative Frequency (%)	No. of Answers
Mucus membranes		
Normal	21	29/57
Congested	69	29/57
Cyanosed	10	29/57
Pale	0	29/57
Icteric	0	29/57
Temperature		
Hypothermia	57	37/57
Hyperthermia	7	44/57
Type of respiration		
Normal	33	39/57
Abnormal	67	39/57
Polypnea	61	36/57
Dyspnea	68	34/57
- Inspiratory dyspnea	6	18/34
- Expiratory dyspnea	94	18/34
Cardiac auscultation		
Normal sounds	78	36/57
Murmur	21	34/57
Arrhythmia (%)	9	35/57
Tachycardia (%)	69	36/57
Bradycardia (%)	6	34/57
Gut sounds		
Absent (%)	20	20/57
Diminished (%)	25	20/57
Normal (%)	50	20/57
Increased (%)	5	20/57
Miscellaneous		
Full bladder on palpation (%)	80	15/57

cases of AM were studied because histologic testing was always performed on postmortem muscle samples.

Young female horses were more frequently affected by AM. This observation must be interpreted in light of the demographic characteristics of horses pasturing in Wallonia, which was the region in Belgium the most affected by AM. It is likely that, in the population of horses kept at pasture, there is a predominance of horses < 3 years of age (the usual age of breaking in), of females rather than males, and of rustic breeds. Breed rusticity did not appear to be a protective factor, however, because breeds such as Belgian Ardennes draft horses, Haflinger and Norwegian Fjord ponies have suffered from AM. Cases involving donkeys have not been reported in the literature so far, although donkeys potentially might suffer from overt AM. Indeed, although no donkey was confirmed for AM in our study, measurement of CK activity in serum of Co-G horses demonstrated that 1 donkey was subclinically affected by AM (CK, 3,720 U/L). Nevertheless, there is no evidence that AM affects any other animal species.

AM showed a temporal occurrence; most cases were observed in autumn. Geographic characteristics of the premises (ie, humid area or area subject to humidity) in which the outbreaks occurred, the characteristics of the pastures (ie, surrounded by or containing trees), the seasonal occurrence of AM (ie, spring and autumn), and the meteorologic topographic data suggest that humidity, no heavy frost, no hot temperature, and organic compounds (ie, leaves or wood) are required for development of AM. This hypothesis is reinforced by the observation of precise climatic conditions associated with clinical occurrence of the disorder. In addition, drastic weather conditions (especially wind) seem to predispose to the onset of clinical signs as has been suspected for a long time.[6,10,13,15,16] As triggering factors, drastic weather conditions might act as a stressor or be a prerequisite for the etiologic agent to be produced or to exert its toxicity. At the level of the animal, unfavorable weather (eg, cold temperatures and stormy weather) might cause stress and induce a metabolic imbalance. At the level of the environment, particular climatic conditions might stimulate or favor the synthesis of toxins by bacteria or fungi or could render pathogens available for ingestion (eg, when wind brings vegetation to the ground). Specific climatic conditions might also be a prerequisite for a plant to exert its toxicity. For example, in certain circumstances, the plant may become more palatable or may undergo certain metabolic changes that induce toxicity. AM could also be multifactorial, and metabolic disturbances and pathogens could act synergistically with environmental stressors to initiate clinical signs of AM.

Until now, outbreaks of AM have been unpredictable. To prevent occurrence of the condition, it is advisable to monitor weather conditions on a daily basis during the at-risk seasons (ie, autumn and spring). For example, the lack of sunshine during the season, an excess of precipitation, or an increase in relative humidity, in association with daily air temperatures between 0°C and 8°C and strong cyclonic conditions would suggest the need to restrict pasturing time, especially when windy conditions are forecasted. On the other hand, analysis of meteorologic data suggests that clinical cases cease to occur after several days of frost, presumably because the cold destroys the etiologic agent or inactivates the toxin. In the case of climatic conditions favorable to development of AM, horses could be temporarily stabled and released at pasture when the temperature has risen above 10°C or after several days of frost.

AM occurred repeatedly in 2 locations over the period considered. Furthermore, from the interviews, it appeared that 5 locations (of 24 with well-known past history) had encountered several deaths of unknown origin in the past (before AM was recognized in Belgium, ie, in autumn 2000). Therefore, once a case has been confirmed in a field, the field should be banned for pasturing at least during autumn and spring. Preventive recommendations are broad and aimed at reducing time spent at pasture during critical seasons. Risk factors for AM should be evaluated by a case-control study to further improve our knowledge of the epidemiology of AM. Results of such a study could

Table 6. Biochemical and hematologic findings in horses confirmed for atypical myopathy by histology.

Parameters	Normal Values	Mean (SD)	Range	No. of Dosages	Comments
Muscle enzymes					
CK (U/L)	50–200	740,864 (1,362,673)	17,550–7,096,000	30/57	Always highly increased
AST (U/L)	200–400	43,771 (85,527)	832–310,000	12/57	High to very high
LDH_{Tot} (U/L)	100–400	96,427 (198,393)	1,985–899,000	19/57	Always highly increased
Iso-LDH	19.1±3.8	20.8 (7.4)	11.0–30.7		The muscle fraction (LDH_5) is always severely increased, whereas the cardiac fraction (LDH_1) may be within the normal range
LDH_1 (%)	26.1±2.9	23.0 (4.2)	14.4–27.5		
LDH_2 (%)	36.3±3.7	26.3 (5.4)	17.7–33.8	7/57	
LDH_3 (%)	14.8±3.2	11.4 (4.8)	6.0–17.4		
LDH_4 (%)	3.6±2.5	18.5 (7.3)	12.0–32.8		
LDH_5 (%)					
Hepatic function					
ALP (U/L)	140–400	946 (479)	270–2,180	22/57	From normal to very high
GGT (U/L)	5–22	35.1 (46.1)	7.0–220.0	22/57	From normal to very high
Sorbitol dehydrogenase (U/L)	<10	84.4 (203.8)	0.0–800.0	15/57	From normal to very high
$Bilirubin_{Conj}$ (mg/L)	0–4.0	4.11 (4.21)	0.0–18.0	19/57	From normal to high
$Bilirubin_{Tot}$ (mg/L)	2–50	33.2 (16.4)	5.0–68.0	21/57	From normal to high
Biliary salts (µmol/L)	5–33	27.3 (47.7)	1.4–164.7	15/57	From normal to high
Renal functions and ions					
Blood urea (mmol/L)	3.3–8.3	10.7 (4.2)	5.7–18.3	10/57	From normal to high
Creatinine (µmol/L)	44–176	165 (91)	69–355	12/57	From normal to high
Ca_{Tot} (mmol/L)	2.5–3.4	2.41 (0.47)	1.31–3.13	22/57	Within the range or hypocalcemia
Ca^{2+} (mmol/L)	>1.50	1.24 (0.16)	0.95–1.54	20/57	Severe hypocalcemia in most cases
Phosphates (mmol/L)	0.969–2.261	2.03 (0.70)	1.01–3.19	16/57	Within the normal range or hyperphosphatemia
Sodium (mmol/L)	130–145	132 (4)	125–137	20/57	Within the normal range or hyponatremia
Potassium (mmol/L)	3.0–4.7	4.16 (1.38)	2.42–8.15	22/57	Within the normal range or hyperkalemia
Chloride (mmol/L)	95–110	96.3 (4.3)	90.0–102.0	11/57	Within the normal range or hypochloremia
Magnesium (mmol/L)	0.739–1.233	0.98 (0.33)	0.57–1.74	16/57	Decreased, normal or increased
Proteins					
Total protein (g/L)	57–69	68.2 (9.8)	53.0–90.0	23/57	From normal to high
Haptoglobin (mg/L)	<500	1 537 (908)	455–3 630	18/57	From normal to very high
Troponin I (ng/ml)	<0.1	12.2 (19.5)	0.2–67.4	14/57	Always detected in serum
Myoglobin (µg/L)	0	866 (426)	398–1 338	4/57	Always detected in serum

Table 6. Continued

Parameters	Normal Values	Mean (SD)	Range	No. of Dosages	Comments
Energetic metabolism					
Triacylglycerols (mmol/L)	<0.97	5.68 (6.19)	0.32–19.80	19/57	From normal to very high
Glycemia (mmol/L)	3.33–5.55	8.80 (3.14)	5.17–17.22	13/57	Borderline (n = 2) or in hyperglycemia
Lactate (mmol/L)	<4	4.98 (4.84)	0.92–15.90	10/57	From normal to very high
Haematology					
Hematocrit (%)	32–48	45.7 (7.1)	32.0–65.0	19/57	From normal to highly increased
Total white blood cells (10^9/L)	6–12	10.22 (4.92)	4.01–22.40	16/57	From leukopoenia to leukocytosis
Lymphocytes (10^9/L)	1.3–4.25	1.96 (1.25)	0.81–5.21	16/57	Decreased, normal, or increased
Monocytes (10^9/L)	0.17–0.85	0.14 (0.14)	0.01–0.53	16/57	Within the normal range
Neutrophils (10^9/L)	3–6	8.18 (5.20)	2.50–21.40	16/57	From normal to highly increased
Eosinophils (10^9/L)	0.16–1	0.06 (0.16)	0.00–0.64	16/57	Within the normal range
Basophils (10^9/L)	0.0–3.0	0.03 (0.03)	0.00–0.10	16/57	Within the normal range
Erythrocytes (10^{12}/L)	5.5–9.5	11.74 (1.76)	7.59–15.10	16/57	From normal to highly increased
$Hemoglobin_{Tot}$ (g/dl)	11–16.5	16.4 (3.0)	11.1–25.5	18/57	From normal to highly increased
Platelets (10^9/L)	100–350	376 (197)	155–960	18/57	From normal to highly increased
Times of coagulation					
Quick (seconds)	8.2–11	14.82 (3.31)	11.00–18.30	5/57	Sometimes slightly increased
APTT (seconds)	37–54	49.4 (14.6)	26.2–64.9	5/57	Sometimes slightly increased
TCT (seconds)	5–21	16.02 (9.34)	9.00–32.20	5/57	Sometimes slightly increased
Arterial blood					
Pao_2 (mmHg)	>85	75.6 (15.6)	56.0–104.0	8/57	From normal to severe hypoxemia
$Paco_2$ (mmHg)	40–47	36.8 (7.0)	28.0–50.0	8/57	From hypocapnea to hypercapnea
pH	7.34–7.44	7.40 (0.06)	7.31–7.48	8/57	Normal
BE (mmol/L)	−2.5–2.5	−2.19 (2.76)	−6.90–2.00	9/57	Normal or base excess
Venous blood					
pH	7.34–7.44	7.35 (0.05)	7.31–7.40	3/57	Slight metabolic acidosis or normal
BE (mmol/L)	−2.5–2.5	−1.57 (2.06)	−3.90–0.00	3/57	Normal or base excess

CK, creatine kinase; AST, aspartate aminotransferase; LDH_{Tot}, total lactate dehydrogenase; Iso-$LDH_{1–5}$, total lactate dehydrogenase isoforms; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; Ca_{Tot} and Ca^{2+}, ionized calcium; APTT, activated partial thromboplastin time; TCT, thrombin clotting time; BE, base excess.

Table 7. Biochemical findings in clinically healthy co-grazing that significantly differed from those of horses confirmed for atypical myopathy by histology.

Parameter	Normal Values	Mean (SD)	Range	Results of the Welch's Test		No. of Dosages
				df	Statistical Significance	
CK (U/L)	50–200	4220 (20,451)[a,c]	261[c]–126,700[c]	29	$P = .003$	38/77
LDH_{Tot} (U/L)	100–400	1502 (2273)[a,c]	554[c]–7940[c]	18	$P = .026$	10/77
ALP (U/L)	140–400	421 (110)[a,c]	200–695[c]	24	$P < .0001$	21/77
Ca_{Tot} (mmol/L)	2.5–3.4	3.02 (0.31)[b]	2.22[c]–3.43	38	$P < .0001$	17/77
Ca^{2+} (mmol/L)	>1.50	1.55 (0.15)[b]	1.10[c]–1.76	37	$P < .0001$	17/77
Haptoglobin (mg/L)	<500	1031 (544)[a,c]	280–2 073[c]	26	$P = .02$	27/77
Troponin I (ng/ml)	<0.1	0.1 (0.1)[a]	0.0–0.4[c]	13	$P < .02$	20/77
Triacylglycerols (mmol/L)	<0.97	0.33 (0.18)[a]	0.05–0.82	18	$P = .0007$	24/77
Glycemia (mmol/L)	3.33–5.55	4.96 (1.87)[a]	3.38–9.75[c]	18	$P = .0007$	10/77

CK, creatine kinase; LDH_{Tot}, total lactate dehydrogenase; ALP, alkaline phosphatase; Ca_{Tot} and Ca^{2+}, ionized calcium.

[a] Superscripts indicate than the mean was statistically higher in horses histologically confirmed for atypical myopathy versus clinically healthy co-grazing horses (Welch's test; $P \leq .02$).

[b] Superscripts indicate than the mean was statistically lower in horses histologically confirmed for atypical myopathy versus clinically healthy co-grazing horses (Welch's test; $P \leq .02$).

[c] Value out of normal range.

provide useful information for more specific recommendations to prevent AM.

No rhabdomyolysis-inducing plants were found in the pastures of CC horses or in those of previous reported cases of AM.[6,12,14–16] On the other hand, as has frequently been reported in the literature,[10,14–16] the quality of the main vegetation found was questionable. For example, *Ranunculus repens* has no forage value and can be poisonous for livestock,[27] whereas the leaves and flowers of certain cyanogenic phenotypes of *Trifolium repens* contain a glycoside that may be potentially harmful for horses.[28] Among the other potential toxic plants for horses,[25] none is known to induce acute rhabdomyolysis syndrome in horses.[29] Furthermore, with the exception of *Ranuclus repens*, none was persistently found on the surveyed premises. *Acer pseudoplatanus* was constantly observed on the premise of CC, but no health hazard is known to be associated with this tree, which is found commonly in Belgium. Although the botanical survey failed to identify any well-known toxic plant, the pastures were of poor quality, and this fact may have caused the horses to eat vegetation that is normally neglected or to overgraze areas spoiled by earth. Horses in poor body condition or with normal weight were found to be more at risk for AM than overweight horses. The large majority of horses in the CC group, however, were in good body condition. AM should not be considered as a condition affecting debilitated animals.

Affected horses died within 3 days (among them, 51% were euthanized) after the onset of clinical signs. No Co-G horse developed AM after having been turned out from the affected pasture for at least 2 days. This observation suggests an acute intoxication process. In situations of clinical suspicion, clinical diagnosis is a crucial forewarning of AM, as the condition tends to occur in the form of an outbreak. Therefore, early recognition of the disease is of paramount importance to prevent AM in horses pasturing at the same period in an at-risk geographic area. In diseased horses, the first signs noted were stiffness and reluctance to move. Pasture companions should be checked for clinical signs when a case of AM is diagnosed on a premise.

AM occurs in a peracute form, although this study confirmed the existence of subclinical cases.[15] All of the affected horses presented with a very similar and dramatic clinical picture that corresponds with the one usually described in the literature.[6–7,14,15,19] The clinical signs were those associated with postural and respiratory muscle destruction. Typical signs (ie, those that occurred in >50% of cases) were weakness, recumbency, myoglobinuria, stiffness, depression, trembling, difficulty getting up and standing up, reluctance to move, sweating, and respiratory distress. Dyspnea was thought to result from respiratory muscle degeneration and was, in most instances, the primary reason for euthanasia. In hospitalized animals, Pao_2 determinations showed that increasing dyspnea was associated with aggravation of hypoxemia.

Affected horses were often hypothermic. The rectal temperature of affected animals usually increased to normal when the horses warmed up after stabling. Pulse and respiratory rates were moderately increased. Pain was frequently considered moderate compared with the pain usually encountered in horses suffering from digestive colic or from exercise-induced rhabdomyolysis. Other authors have reported that AM-affected horses were in severe pain.[3,14] On rectal palpation, a distended bladder was usually found. Emptying the bladder usually helped to alleviate the observed pain. Bladder distention may have been responsible for the signs of colic that have been occasionally observed, and management of affected horses should include regular emptying of the bladder. Apart from the aforementioned typical signs, several owners and veterinarians have reported that, despite the dramatic clinical picture, some horses still tried to eat. Usually, swallowing seemed

laborious because of profound weakness or dysphagia, and in a few cases, swallowing was impossible because of esophageal obstruction.

Dark-colored urine observed during spontaneous voiding or obtained after rectal palpation may be a key observation contributing to the diagnosis of AM. However, the presence of normally colored urine does not exclude AM. In 2 CC horses, the collected urine was clear, presumably because myoglobin had not yet been excreted in sufficient amount to color the urine, and in 1 CC horse, myoglobinuria resolved on day 3, presumably because muscular destruction had ceased. For this reason, the term myopathy was preferred to myoglobinuria to define the condition, as former refers to the underlying pathologic process rather than to a possible clinical signs (ie, myoglobinuria). The hemorrhagic diathesis inconsistently reported in the literature[6,7] was sometimes observed in the CC horses in this study.

Biochemical and hematologic findings are consistent with those reported in the literature.[5–7,10,12–16] The most remarkable biochemical changes were the increased activities of muscle serum enzyme activity, which indicated massive acute muscle damage. In CC horses, clinical signs were always associated with CK activity, largely >10,000 U/L but sometimes 100,000 to 1,000,000 U/L. Measurement of CK activity was the most useful laboratory test to indicate extensive muscle damage in CC horses. Activity of AST increases less rapidly to peak values than does CK.[30] In 1 CC horse sampled within an hour after the onset of clinical signs, CK enzyme activity was largely out of range, whereas AST activity was only increased slightly. However, when followed over time, CK enzyme activity did not always correlate closely with the deterioration of clinical signs; some horses had lower CK activity before dying than measured in previous samples. High serum CK enzyme activity was found in a few Co-G horses, thus confirming the existence of subclinical cases of AM.[15] When a horse contracts AM, it is advisable to stable the remaining pasture companions until the end of the season. One of the horses with subclinical AM had serum CK enzyme activity higher than the lowest activity found in CC horses (126,700 U/L vs 17,750 U/L, in 1 Co-G horse and 1 CC horse, respectively). This observation challenged the role of serum CK activity as a prognostic indicator, as previously proposed.[6] Only 1 pasture companion showing signs of AM survived. Whether or not this nonfatal exposure to the causative agent of AM induces resistance to the condition is unclear. Data about this horse were not included in this study because it did not match case selection criteria for the CC or Co-G group. AM appeared as a peracute condition that was almost always fatal once clinical signs were present. Troponin I was constantly increased in the serum of AM-affected horses, which suggests that myocardial damage is associated with clinical episodes of AM. However, cardiac dysfunction and visible myocardial lesions at necropsy were not consistently found either in CC horses[18] or reported in previous published studies.[6,11] The apparent discrepancy between myocardial damage, as measured with troponin I, and the absence of myocardial lesions in some cases of AM[6,18] probably reflects the difficulty of making an accurate histopathologic assessment of the heart with randomly collected samples (ie, visible myocardial lesions are not consistently found at necropsy[6,11,8]). Because of extensive muscle damage and involvement of the myocardium, the question is raised about the recovery of horses clinically affected with AM. Troponin I was also detected in the serum of some Co-G horses.

Hypocalcemia was present in most of the CC horses and in some of the Co-G horses. The low calcium concentration may have contributed to the muscle weakness and to the dysphagia and esophageal obstruction observed in a few CC horses. Other biochemical derangements characteristic of severe muscle damage, such as hyperphosphatemia, hyponatremia, hypochloremia, and hyperkalemia, were not consistently found in CC horses or in other reported cases of AM.[10,14] These changes are usually attributed to renal damage secondary to myoglobinuria, but blood urea and creatinine concentrations did not always indicate renal failure. The horses may have died too quickly for muscle damage to have had time to induce renal failure.

Observation of high concentrations of serum triacylglycerols in conjunction with neutral lipid accumulation in degenerated muscles (as demonstrated by histology[14,18]) suggests a metabolic myopathy caused by a failure in energy production related to a defect in lipid oxidation metabolism. On the other hand, there is no evidence of any glycolytic enzyme deficiency.[18] It may be advisable to supply energy to horses with AM by providing carbohydrates (CC horses usually behaved as if they were starving). However, the frequently found hyperglycemia suggests that carbohydrate supplementation should be provided by oral rather than parenteral administration in conjunction with insulin administration.

Serum activities of liver enzymes were of limited diagnostic value (normal to very high activities). On the other hand, changes in enzyme activities often revealed severe alterations of hepatic tissue. The biochemical changes associated with hepatic injury tended to worsen with time.

Therefore, the most diagnostically useful biochemical test was the measurement of serum CK enzyme activity and troponin I to confirm the presence of skeletal and cardiac muscle damage, respectively. Other biochemical tests may be of interest to guide treatment, which may only be symptomatic, the cause of the condition being so far unknown.

Conclusions

AM is a sporadic seasonal disease closely related to meteorologic conditions. At the beginning of high-risk seasons, close monitoring of meteorologic conditions may decrease the number of AM outbreaks. Measures could then be taken to reduce pasturing time in fields with poor drainage characteristics, when the weather is very wet and rather cold for several days, and when windy conditions are forecasted.

Not all horses have the same risk of developing AM; thus, strategic preventive measures should target young horses that appear to be at risk for the condition. Strict removal from pasture is recommended for Co-G horses that develops signs of AM. Pasture companions should be checked for any clinical signs suspicious of AM as well as for increased muscle enzyme activity for at least 48 hours. Once a case has been confirmed, the location should be banned from pasturing, at least during autumn and spring.

Diagnosis of AM should be suspected in pastured horses that have a sudden onset of clinical signs reflecting acute destruction of respiratory and postural muscles and production of dark-colored urine. Measurement of serum CK activity in diseased horses and healthy pasture companions will confirm or eliminate the diagnosis and will help detect subclinically affected horses. Management of AM horses includes warming when hypothermia is found. Intensive fluid therapy is advised as well as regular emptying of the bladder. Supportive treatment includes carbohydrate supplementation with concurrent insulin administration. The decision for euthanasia should be based on the severity of respiratory signs rather than serum CK activity, which appears to be of poor prognostic value.

Footnotes

[a] GPS, eTrex Venture, Garmin Europe, Ltd, Hampshire, UK

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