

In: **IVIS Reviews in Veterinary Medicine**, I.V.I.S. (Ed.). International Veterinary Information Service, Ithaca NY (www.ivis.org), Last updated: 15-nov.-2006; R0101.1106

Atypical Myopathy (Atypical Myoglobinuria)

D. M. Votion¹, **H. Amory**², **V. Demoulin**³, **D. Desmecht**⁴, **F. Rollin**⁵, **E. Thiry**⁶ and **E. Baise**⁷

^{1,12} Department of Infectious and Parasitic Diseases, Bacteriology and Pathology of Bacterial Diseases; ^{2,5,9,11} Department of Clinical Sciences, Large Animal Internal Medicine; ³ Department of Life Sciences, Algology and Mycology, Faculty of Sciences; ^{4,7} Department of Morphology and Pathology, General Pathology; ⁶ Department of Infectious and Parasitic Diseases, Virology, Epidemiology and Pathology of Viral Diseases; ⁸ Department of Morphology and Pathology, General Pathology and Autopsy; ¹⁰ Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Liège, Liège, Belgium.

Summary

D.M. Votion

Introduction

D.M. Votion and A. Linden

Diagnosis of Atypical Myopathy (Atypical Myoglobinuria)

D.M. Votion, F. Rollin, C. Sandersen, C. Delguste, A. Linden and H. Amory

Postmortem Examination

D. Cassart, E. Baise and D. Desmecht

Etiological Hypotheses

D.M. Votion, V. Demoulin, E. Piat and A. Linden

Epidemiology

C. Delguste, E. Thiry, E. Piat, A. Linden and D.M. Votion

Submission Forms

Summary

D.M. Votion

Atypical myopathy, also called "atypical myoglobinuria", is a frequently fatal myopathy of unknown origin occurring sporadically in grazing horses. The condition has been reported in several European countries and case reports prior to the syndrome's identification suggest that the condition has also been encountered in Australia, Canada and United States of America. The main feature of this syndrome is the sudden onset of clinical signs characterized by muscular weakness, stiffness, recumbency, sweating and when urine is observed, myoglobinuria. The biochemical test most useful towards diagnosis is the level of serum muscle enzymes activities which confirms the presence of severe muscle damage. The definite diagnosis is based on specific histological findings in the affected muscles (i.e., usually postural and respiratory muscles and occasionally, heart muscle).

A few etiological hypotheses have been investigated but, so far, the cause of atypical myopathy remains unknown. It is suspected that the condition is induced by an ingested or enterically produced toxin (e.g., bacterial toxin, mycotoxin or phytotoxin). Nutritional myopathy might also play a role in the pathogenesis of the syndrome. Whatever the cause, particular weather conditions seem to trigger the appearance of clinical signs. Thorough epidemiological studies are required to make recommendations for prevention and until the etiology is found, only symptomatic treatments may be recommended.

Introduction

D.M. Votion and A. Linden

Atypical myopathy is an acute myopathy of postural, respiratory and occasionally cardiac muscles that appears in an epizootic or sporadic form in grazing horses. As opposed to exertional rhabdomyolysis, this frequently fatal myopathy occurs independently of muscular exercise but seems to be triggered by particular climatic conditions. Atypical *myopathy*

has also been called atypical *myoglobinuria*, however, the former name is preferred in this work because it refers to the underlying pathological process rather than to one of its possible clinical signs, i.e., myoglobinuria.

To the authors' knowledge, the first case reports of myopathy in grazing horses concerned outbreaks that occurred in the fall of 1939 in the North of Wales, Great Britain [1]. The history, clinical manifestations, postmortem findings and histological lesions from affected muscles were indeed highly suggestive of atypical myopathy. Other case reports compatible with atypical myopathy have since sporadically been reported in the literature [2-4]; see Table 1a. Previous to these publications, a condition that bore some resemblances to atypical myopathy and was named *enzootic hemoglobinuria with dysphagia or enzootic myoglobinuria* has been described in old veterinary medicine books [5,6]. It may therefore be suggested that atypical myopathy is not a new syndrome even if it was identified as a specific entity for the first time in 1984 at a meeting held in Edinburgh [7]. This urgent reunion had been organized in reaction to concurrent cases of myopathy occurring that year in various parts of Scotland [8,9]. Since the syndrome's recognition, outbreaks of atypical myopathy have been reported in several European countries; see Table 1b. Occurrence of the condition has been unpredictable: On one hand, there may be no cases recorded from year to year in an area where atypical myopathy has been diagnosed previously [10], on the other hand, a large number of cases may suddenly occur in an area, zone and/or country not affected in the past. For example, in the fall of 1995, a large number of horses (i.e., more than one hundred) died from atypical myopathy in Northern Germany where the syndrome had not been diagnosed before [11]. In Belgium, two large outbreaks were recorded during the cold seasons of the years 2000 [12] and 2002 (Delguste and Votion, unpublished data) whereas only two cases were encountered in spring 2001 [12]. In the fall of 2002, atypical myopathy was reported in the north-east of France, where it was seen for the first time [13].

Table 1. Reported Outbreaks of Myopathy in Grazing Horses (a) before and (b) after Recognition of Atypical Myopathy as a Specific Entity					
Author(s)	Country	Year(s) of Onset	Season	Mortality	Age (Range)
A					
Bowen and Craig, 1942 [1]	Great Britain	1939	Fall	5/6	6 months to 3 years
Irwin and Pulsford, 1951 [14]	Australia	1951	Fall	1/1	2 years
Pope and Heslop, 1960 [2]	Canada	1959	Fall	1/3	5 months to 10 years
Tritschler and Miles, 1966 [3]	USA	1965	Fall	5/8	4-7 years
Carthé et al., 1976 [4]	Belgium	1975 1976	Fall Winter	3/4	7 months
Hosie et al., 1986* [9]	Ireland	1982	Fall	3/3	2-3 years
B					
Anonymous, 1985** [7]	Great Britain	1972 & 1984	Not defined Fall	25/27	Foal to 11 years
Hosie et al., 1986 [9]	Scotland	1984-1985	Fall Winter/Spring	8/12	1.5-6 years
Whitwell et al., 1988 [15]	England	1985	Spring	4/4	2-14 years
Harris and Whitwell, 1990 [10]	England	1990	Fall	Not defined	Not defined
Robinson, 1991 [16]	England	1990	Not defined	0/2	Not defined
Hillam, 1991 [17]	England	1990	Not defined	1/1	1.5 years

Author(s)	Country	Year(s) of Onset	Season	Mortality	Age (Range)
Brandt et al., 1997 [11]	Germany	1995-1996	Fall Winter/Spring	111/115	1.5-16 years
Delguste et al., 2002+ [12]	Belgium	1998	Fall	1/1	4 years
Delguste et al., 2002 ° [12]	Germany Great Britain Ireland Switzerland Denmark Lithuania	Not defined	Not defined	± 40 cases: mortality not defined †	Not defined
Delguste et al., 2002 [12]	Belgium	2000-2001	Fall	14/14	6 months to 11 years
Moussu et al., 2003 [13]	France	2002	Fall	56/67	< 3 year for 50%
Votion et al., 2003a [18]	Belgium	2003	Spring Fall/Winter	3/3	2-8 years
Total mortality (published records):				241/271 (†: 40 cases excluded) Mortality rate: 89%	
<p>*Personal communication from Power E.P. to Hosie B.D **Some horses in this report may have been included in the Hosie's study (1986) +Personal communication from the University of Gent to Delguste C. °Personal communication from various European faculties of veterinary medicine to Delguste C.</p>					

This manuscript will review the literature on atypical myopathy in order to gather all the available information relating to this syndrome. The main objectives are: (1) to offer all equine practitioners and clinicians of referral centers a detailed description of the condition, that will hopefully be of assistance in the diagnosis of atypical myopathy; (2) to discuss the etiological hypotheses suggested in the reviewed papers; (3), to propose an epidemiological questionnaire that will enable the collection of invaluable data which are required to determine risk factors and find preventive measures and, (4) to propose a clinical questionnaire that will enable a consensual description of the syndrome. Atypical myopathy outbreaks are of an acute and unexpected nature, which often means that complementary examinations and epidemiological investigations might be overlooked. It is therefore hoped that the information given in this document will aid practitioners in the recognition and handling of a suspected case.

Diagnosis of Atypical Myopathy

D.M. Votion, F. Rollin, C. Sandersen, C. Delguste, A. Linden and H. Amory

A presumptive diagnosis of atypical myopathy is based on history, clinical signs, laboratory findings and postmortem examination. The definite diagnosis is based on specific histological findings in the affected muscles (i.e., usually postural and respiratory muscles; see the section on "Postmortem Examination"). The most important clues from the history, clinical signs, laboratory findings and postmortem examination that suggest a diagnosis of atypical myopathy are summarized in Table 2.

Table 2. Factors Contributing to the Diagnosis of Atypical Myopathy			
History	Clinical Signs	Laboratory Findings	Postmortem Examination
Grazing horses (grass being the main part of alimentation)	Muscle weakness and stiffness	Huge increase of muscle enzymes activities in serum	No other evident cause of death
Sudden onset of clinical signs	Sudation and muscle tremors	Increase of cardiac enzymes activities in serum	No significant gross lesions
Several animals affected	Recumbency	Hypocalcemia	Postural, respiratory and cardiac muscle discoloration
Clinical series	Tachypnea and dyspnea	Myoglobinemia	
Fall +++ Winter ++ Spring +	Rapid degradation of clinical signs		Histological Findings
Particular climatic conditions	Animal not anorexic (but may be dysphagic)		Degenerated fibers in postural and respiratory muscles
Animal found dead during atypical myopathy outbreaks	Little or no evidence of pain		Necrosis of type I fibers
	Myoglobinuria		
	Tachycardia		
	Horses afebrile		
	Full bladder on palpation		
	Quick death (usually within 3 days)		

History

Atypical myopathy has only so far affected horses kept mostly at pasture during the cold months of the year. The most remarkable feature of the syndrome was the sudden onset of clinical signs. The outbreaks often seemed to be triggered by particular climatic conditions. Reported cases concerned one or several horses in a group of grazing horses and the affected areas varied from very restricted geographical zones [2-4] to large regions [7,11-13].

Animals

Horses, draft horses and ponies of various breeds and both sexes have suffered from atypical myopathy. Breed rusticity did not appear to be a protective factor [12]. Cases involving donkeys have not been reported in the literature so far. The condition seemed to affect young animals predominantly; however, it has also been reported in adult horses [13]. In general, affected horses were in good body condition [2,9,15,19]; Fig. 1.



Figure 1. Pony belonging to a group that has several times been affected by atypical myopathy. Clinical cases and co-grazing companions were in very good health at the onset of outbreaks. - To view this image in full size go to the IVIS website at www.ivis.org . -

Pasture

All the clinical cases reported in the literature were affected while at pasture except for two horses who had been stabled the day before the appearance of clinical signs [9,12]. Most horses had been at pasture for weeks to months with only a few cases receiving supplementary feed before the onset of clinical signs [2,9,15,19]. Grazed pastures were of variable quality [9] but usually, they were particularly bare [1,3,15]. Many of the affected fields contained and/or were bordered by trees [2,11,12,15] (Fig. 2a, Fig. 2b, and Fig. 2c). The presence of dead wood and/or fallen branches brought down by storms has

been mentioned [7].



Figure 2a . Pastures in Belgium where atypical myopathy cases were diagnosed in the fall of 2002. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 2b. Pastures in Belgium where atypical myopathy cases were diagnosed in the fall of 2002. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 2c . Pastures in Belgium where atypical myopathy cases were diagnosed in the fall of 2002. - To view this image in full size go to the IVIS website at www.ivis.org . -

Seasons

Atypical myopathy seems to have a temporal occurrence with most cases having been observed in the fall. The higher incidence of cases during fall may be linked to the weather encountered during this season. However, it is difficult from the literature to point out a specific feature of the meteorological data. Depending on the outbreak, the weather prior to the onset of the clinical syndrome was described as "very wet and cold" [2,15,17], "colder" [3], "stormy and cold" [4], "stormy, cold and humid" [9] or "stormy and humid" [12]. Whatever the common factor, if such a factor exists, unfavorable climatic conditions appear to play a role in the pathogenesis of atypical myopathy.

This "trigger factor" may be working at one or both of the following levels: it may act directly on the animals (e.g., cold temperatures and bad weather causing a stress) and/or the environment (e.g., by rendering pathogens available for ingestion when the wind brings vegetation to the ground or by providing specific conditions required to the production of bacterial or fungal toxins...).

Miscellaneous

A large majority of reported cases had not been exercised prior to the onset of acute myopathy [11]. However, some cases had been exercised immediately before the occurrence of clinical signs [3,18]. Generally, when only one of several exercised horses develops clinical signs of acute myopathy, the diagnosis of exertional rhabdomyolysis should be considered [18]. On the other hand, when several of the exercised horses simultaneously present clinical signs of acute rhabdomyolysis, atypical myopathy is more likely. It should be emphasized that atypical myopathy frequently breaks out as clinical series [9,12,13].

Clinical Signs

Horses affected by atypical myopathy presented sudden muscle weakness and stiffness. They were reluctant or unable to move and most of them quickly adopted lateral recumbency. Sudation and muscle tremors were frequently observed, whereas muscle tenseness and hemorrhagic diathesis were inconsistently mentioned [7,9]. Dyspnea and tachypnea were often reported. Recumbency and respiratory distress are thought to be the result of postural and respiratory (e.g., intercostals and diaphragm) muscles degeneration, respectively; see "Postmortem Examination". Respiratory difficulty progressed with time and was frequently the main reason for euthanasia. Despite this dramatic picture, horses were rarely anorexic. The animals had a good appetite even if swallowing seemed difficult or, in a few cases, impossible due to esophageal obstruction [11,12]. Some authors were surprised by the apparent lack of pain despite the severity of the clinical signs and the extent of muscle damage as demonstrated by the activity of muscle enzymes in serum [7,15]. On the contrary, other authors reported that the affected horses seemed to be in severe pain [2,11]. When observed, the emission of dark colored urine (Fig. 3) was the most suggestive sign of myopathy. Exceptionally, clear urines may be observed (presumably because myoglobin has not yet been excreted in sufficient amount to color the urines or, if muscular destruction has ceased). In the final stage, a few horses also showed signs of icterus [1,17,18].



Figure 3. Urine sample collected from a horse suffering from atypical myopathy. - To view this image in full size go to the IVIS website at www.ivis.org . -

The clinical examination also frequently revealed tachycardia. Occasionally, cardiac arrhythmias and/or heart murmurs were found [11,12]. Horses were in hypothermia or had a rectal temperature within the normal range [11,12].

When performed, rectal palpation revealed a highly distended bladder in several horses [11]. This distension might be responsible for the signs of colic that have been occasionally observed.

As the etiology of atypical myopathy is still unknown, therapeutic approaches may only be of supportive nature and therefore will not be developed in this work. The aim of the treatment should be to limit pain and further muscle damage, to correct biochemical abnormalities, to maintain a normal hydration status and to prevent renal compromise.

Once signs of the syndrome are present, the prognosis is very poor whatever the treatment. From the literature review, a mortality rate of 89% has been calculated, horses frequently dying within three days [9,11,12,15,19]. Respiratory failure and/or cardiac damage were the suspected possible causes of death [3,4,15] or the reason for euthanasia [18].

Concerning the cases that survived, convalescence took a long time. Very few fully recovered and returned to training, whereas others surviving cases showed extensive muscle wastage [4,7,9].

Laboratory Findings

Biochemical and hematological findings of horses affected by atypical myopathy and reported in the literature are summarized in Table 3.

Table 3. Biochemical and Hematological Findings		
Parameters	Results	References
CPK	Very high values	[4,7,11,12,9,15,16-18]
AST	Inconclusive	[3]
	High to very high values	[4,7,11,12,9,15,18]
LDH _{Tot}	Very high values	[4,11,12,18]
aHBDH	Very high values	[11]
ALT	High values	[4]
PAL	High values	[12]
GGT	Within the normal range or (slightly) elevated	[11,9,15]
	Increased	[12]
SDH	Within the normal range or slightly elevated	[9]
	Slightly to severely elevated	[12,15]
Calcium:		
<i>Total</i>	Hypocalcemia	[9,15]
	Within the normal range or hypocalcemia	[11,18]
<i>Ionized fraction</i>	Hypocalcemia	[12,18]
Blood urea	Within the normal range	[2,3]
	Moderately raised	[7,9,15]
	Within the normal range or slightly increased	[11,12]
Creatinine	Inconclusive	[3]
	Within the normal range	[15]
	Within the normal range or (slightly) increased	[11,12]
Glycemia	Hyperglycemia	[11]

Lactate	Hyperlactatemia	[11]
Total protein	Within the normal range or hyperproteinemia	[12,15]
Phosphate	Within the normal range or hyperphosphatemia	[15]
	Hyperphosphatemia (n=1)	[12]
Sodium	Within the normal range or hyponatremia	[12,15]
	Within the normal range or hypernatremia	[11]
Potassium	Within the normal range or hypercalemia	[12,15]
	Within the normal range	[11]
Chloride	Hypochloremia	[15]
	Within the normal range or hyperchloremia	[11]
	Within the normal range or hypochloremia	[12]
Magnesium	Decreased, normal or increased	[11]
	Slightly increased	[12]
T3/T4	Within the normal range	[11]
Troponin T	High (n=7) or normal (n=1) values	[11]
pH	Metabolic acidosis or normal pH	[11]
	Slight metabolic acidosis (n=1)	[12]
Base deficit/excess	Normal or base excess	[11]
	Base excess (n=1)	[12]
Hemoglobin concentration	Within the normal range	[2]
	Increased	[9,12]
	Within the normal range or increased	[11]
Hematocrit	Increased	[9]
	Decreased, normal or increased	[11]
	Normal or increased	[12]
White blood cell:		
<i>Count</i>	Within the normal range	[2]
	Slight to significant leukocytosis	[9]
	Leukocytosis (n=1)	[15]
	Within the normal range or (slight) leukocytosis	[11,12,19]
<i>Formulae</i>	Neutrophilia with or without lymphopenia	[9]
	Neutrophilia (n=1)	[15]
	Normal or neutrophilia with lymphopenia	[11]
	Normal or neutrophilia without lymphopenia	[12]
<i>Morphology</i>	Slight shift to the left	[2,11]
See text for signification of abbreviations		

Biochemistry

The most striking changes concerned the increased activities of muscle enzymes in serum that indicated massive acute muscle damage: serum activities of creatine phosphokinase (CPK), aspartate aminotransferase (AST) and total lactate dehydrogenase (LDH_{Tot}) were always highly increased. In several cases, CPK values attained hundreds of thousands or even exceeded the million international units per liter [9,12,16]. It has been suggested that serum CPK levels might be of prognostic value [9], however, horses with subclinical atypical myopathy may have higher CPK values than those found in some fatal cases (Delguste and Votion, unpublished data). All pasture-companions should be removed from the pasture where a diagnosis of atypical myopathy is suspected. Serum activities of muscle enzymes should be determined in these co-grazings. This might enable the detection of subclinical cases which should be monitored for several days and/or which should receive appropriate medical care.

Serum activities of liver enzymes such as alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ -glutamyl transferase (GGT) and sorbitol dehydrogenase (SDH) were either within the normal range or slightly to severely elevated.

When the ionized fraction of calcium was measured, hypocalcemia was always found. Other biochemical derangements characteristic of severe muscle damage such as hyperphosphatemia, hyponatremia, hypochloremia and hypocalcemia [20] were not constantly reported. In fact, these changes are usually attributed to renal damage secondary to myoglobinuria but renal lesions were not always detected at postmortem in horses dying from atypical myopathy (see "Postmortem Examination"). Blood urea and creatinine did not demonstrate extreme changes. From these results, it may be concluded that affected horses did not die from muscle damage-induced renal failure [2].

Supplementary tests performed by Brandt and collaborators [11] included the dosing of active iodothyronines, i.e., triiodothyronine (T3) and thyroxine (T4). Hypothyroidism has controversially been suggested as a contributory factor in certain muscular problems in horses [21]. Results of these dosages were within the normal range but a more accurate diagnosis of hypothyroidism should rely on TSH or THR stimulation tests. Such tests are difficult to justify in the clinical context of atypical myopathy. Hyperglycemia and significant lactatemia were constantly found [11]. Stress and pain are well-known common causes of hyperglycemia. Brandt and collaborators also measured the activity of the myocardial enzyme α -hydroxybutyrate dehydrogenase (α HBDH) and the muscle protein troponin T, the latter including skeletal and cardiac isoforms. All tested horses had very high values for α HBDH and all but one horse had high values for troponin T.

Several authors determined the selenium, glutathione peroxidase and vitamin E levels. Results of these dosages will be discussed below (see Etiological Hypotheses: Nutritional Myopathy).

Hematology

Hematological alterations were not consistently present; when leukocytosis was observed, it always resulted from neutrophilia with or without lymphopenia [9,11,12,15]. A slight left shift, indicating the presence of increased immature neutrophils in the circulation, was also reported [2-4,7,11].

Urine Analysis

Urine analysis is of limited value due myoglobinuria which increases urine opacity (see Fig. 3), this opacity interfering with several methods of testing. In addition, many dipsticks may not differentiate myoglobin from hemoglobin. When appropriate methods of dosage were used, the examination of urine samples revealed traces of albumin, hemoglobin and a large amount of myoglobin [2,3,7,9,12]. From biochemical findings and urine analysis, there was no evidence of kidney failure [4,15].

Differential Diagnosis

Differential diagnosis of sudden muscular weakness, severe myopathy and/or unexpected death includes several neurogenic and myopathic disorders [22]. The main pathologies that share clinical similarities with atypical myopathy include the acute form of grass sickness, botulism, the equine rhabdomyolysis syndrome, the hyperkalemic periodic paresis, several toxic myopathies induced by plants or drugs (see "Etiological Hypotheses"), nutritional myopathy (see "Etiological Hypotheses - Nutritional Myopathy"), postanesthesia myopathy, tetanus and possibly, acute piroplasmiasis. Collection of history may easily rule out some of the potential diagnoses (e.g., equine rhabdomyolysis syndrome when a group of unsupplemented pastured horses present simultaneously clinical signs of myopathy...) or may suggest an etiological hypothesis (e.g., drugs intoxication with ionophores if the animal had accidentally had access to poultry or ruminant foodstuffs, postanesthesia myopathy when clinical signs follow anesthesia, equine rhabdomyolysis syndrome when clinical signs have been triggered by exercise...).

The differential diagnosis relies also on accurate observation of clinical signs. In tetanus, prolapsed nictitating membrane, limbs extension and convulsions exacerbated by external stimuli contribute to the diagnosis whereas poor eyelid (also found in grass sickness), tail and tongue tone favour the diagnosis of botulism. In both diseases, myoglobinuria is not

observed. As in atypical myopathy, dysphagia may be encountered in tetanus, botulism and grass sickness. Myopathies induced by plants have been reported in America but the implicated plants do not occur in Europe (see "Etiological Hypotheses"). Intoxications with European plants that may mimic signs of atypical myopathy include Horsetail (muscle tremors, reluctance to move and weakness), Bracken and Sensitive Ferns (weakness) and *Taxus* (sudden death) poisoning. These plants are easily recognizable; they do not induce myoglobinuria. Color of urine observed during spontaneous emission or obtained following rectal palpation may also contribute to exclude some hypotheses (e.g., botulism, tetanus, grass sickness...) and reinforce the diagnosis towards a myopathic process, however, it may not differentiate from hemolytic anemia. When present, jaundice and anemia greatly contribute to the diagnosis of piroplasmiasis (these clinical signs are not found in atypical myopathy). Very high level of muscle enzymes activity will only be found in severe myopathies and therefore contributes to exclude other disorders (e.g., botulism, tetanus, grass sickness...). Therefore, the dosage of serum CPK activities is of particular interest. However, it should be emphasized that mild to moderate elevation in the activities of serum CPK may be found in recumbent horses because of muscle alteration induced by muscles crushing. Diagnosis of atypical myopathy should not be considered when CPK values remain below 10,000 IU/L [23]. Outbreaks of myopathies that seem triggered by particular climatic conditions in autumn or spring strongly suggest a diagnosis of atypical myopathy.

Conclusion

The main facts contributing to the diagnosis of atypical myopathy are (1) the sudden onset of typical but non pathognomonic clinical signs of severe myopathy (2) in one or several horses within a group of grazing horses, (3) following particular climatic conditions. The most diagnostically helpful biochemical test is the measurement of serum CPK activity to confirm the presence of severe muscle damage. Other biochemical tests may be of interest to direct treatment which may only be symptomatic, the cause of the condition being unknown. The definite diagnosis is based on specific histological findings in the affected muscles (i.e., usually postural and respiratory muscles and occasionally, heart muscle).

Postmortem Examination

D. Cassart, E. Baise and D. Desmecht

Necropsy Findings

Unfortunately, necropsy was not conducted on all horses for which a diagnosis of atypical myopathy was suspected. The most constant feature reported was the presence of dark brown (typically coffee-colored) urine in the bladder. Generalized congestion was also noticed [12]. Modifications of the kidneys were sometimes observed including: yellowing of the cortex [1], yellowing of the medulla [9], dark or pale kidneys [4], occasionally dark strips in the medulla [3] or patchy congestion [10].

Esophageal impaction was rarely reported [3,12]. The stomach content was usually normal [3], however, areas of erosion or ulceration were often observed in the gastric mucosa [7,9,10,11] (Fig. 4) sometimes associated with a small amount of serohemorrhagic content [12]. No specific gross lesion was ever seen in the intestinal tract; sometimes the small intestine was empty [3], in another report, petechial hemorrhages were seen in the intestinal mucosa [9] and in one case report, acute enteritis with a serohemorrhagic content as in proximal enteritis was described [12]. Other non specific lesions, such as parasitism, were occasionally found in the gastrointestinal tract. The only gross lesion affecting the liver was diffuse fatty degeneration [3,11,12] (Fig. 5).



Figure 4. Ulcers in the gastric mucosa. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 5. Fatty degeneration of the liver. - To view this image in full size go to the IVIS website at www.ivis.org . -

Lungs were generally congestive [4,7,10] and sometimes edematous, with the bronchial tree full of froth [3,12]. Hemorrhagic petechiae and ecchymoses were occasionally noticed on several serosal membranes including: the perirenal [3], visceral subpleural [3,7,9,12], parietal pleural [7,12], diaphragmatic [9], meningeal [12] and the epicardial serosa found on the coronary grooves [10]. The same lesions were also noticed within the myocardium [3,7,9] and skeletal muscles [1,10]. One case of aortic rupture with a hemopericardium was reported [9]. The myocardium was sometimes either extremely pale (or had pale areas [3,12]; Fig. 6) or presented intramural hemorrhages [7,9]. The localization of the lesions

was described in a few cases: for example, pallor in left ventricle [10], stippling of the myocardium [10,12] and for one case, fibrous tissue was present on the epicardium [10]. One case of hydropericardium was reported [12].



Figure 6. Pale areas in the heart sectioned at the level of the left ventricle. - To view this image in full size go to the IVIS website at www.ivis.org . -

In some cases, the absence of gross lesions within skeletal muscles was noticed [7,12]. In one report, only congestion and edema were seen in the neck, back and loin muscles [7] and in another report in the neck and forelimbs muscles [9]. In other reports, the description of gross lesions observed in several striated muscles included pallor, yellowing, presence of pale areas or a "fish-like" appearance with some hemorrhagic patches [1,3,11]. Macroscopically affected muscles were specified by some authors: the crural muscles, psoas magnus, gluteus, infraspinatus, supraspinatus, seratus magnus, and subscapularis in one report [1]; the rectus femoris, infraspinatus, supraspinatus, multifidus cervicis and other deep cervical muscles in a later report [3] and finally, abdominal muscles, tongue, diaphragm and intercostals in more recent reports [15,18]. For example, changes involving discoloration in postural and respiratory muscles are shown on Fig. 7a and Fig. 7b.



Figure 7a. Muscle discoloration observed in shoulder muscles. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 7b. Muscle discoloration observed in intercostals. - To view this image in full size go to the IVIS website at www.ivis.org . -

Histological Findings

On histology, renal damage was a constant feature. Nephrosis and degeneration of the epithelial lining with proteinaceous casts deposition affected the convoluted tubules and collecting ducts mainly [7,9]. In the kidneys, many tubules contained bright red granular casts with some free pyknotic cells and sometimes pink proteinaceous granular material was present in Bowman's spaces around glomeruli [9,15]. In other reports, myoglobinuric cylinders were observed in tubules without any other evidence of degeneration [11,12] (Fig. 8), except in one case where tubular necrosis was observed [11].



Figure 8. Myoglobinuric cylinder in renal tubule from a fatal atypical myopathy case. Hematoxylin and eosin; magnification x 400. (With the permission of the "Annales de Médecine Vétérinaire" © [12]). - To view this image in full size go to the IVIS website at www.ivis.org . -

Lesions from parasitism were sometimes observed on the alimentary tract mucosa [15] but these lesions are non significant for myopathy. Acute gastritis was noticed [11], sometimes with mucosal erosions [12]. Hypercontraction bands were occasionally seen on smooth muscle fibers of the stomach and small intestine [12]. In the liver, the most frequent histological lesion was a patchy vacuolation; some cells containing many vacuoles [11,12,15]. This lesion was often described as fatty degeneration [11,12].

In the lungs, congestion and edema were often present (Fig. 9), sometimes accompanied by an alveolar macrophage response [15] or by hemorrhagic petechiae and ecchymoses [12].



Figure 9. Congestion and edema in the lung section from a fatal atypical myopathy case. Hematoxylin and eosin; magnification x 100. (With the permission of the "Annales de Médecine Vétérinaire" © [12]). - To view this image in full size go to the IVIS website at www.ivis.org . -

Forebrain swelling with cellular edema was reported in 3 cases; however, these lesions are not pathognomonic and suggest

the presence of toxemia [7]. Other lesions affecting the central nervous system included little hemorrhage foci on the meninges [12,15].

Some lesions (vacuolation, hemorrhages and necrosis) were noticed in adrenal glands [15].

According to some authors, no histopathological changes were present in the cardiac muscle [7,9]. However, other authors described the presence of degenerative lesions in the myocardium [11,12] sometimes with hemorrhagic patches [12]. Some myocardial samples showed microscopic changes; individual or small groups of cardiac fibers were more brightly stained than normal and had lost their striations. The nuclei of such fibers often appeared pyknotic. Sometimes there were many small foci of muscle degeneration and this was accompanied by an inflammatory cellular infiltration [15].

The most constant and typical histopathological lesions are the result of degeneration of striated muscles. This sometimes appeared as macroscopic lesions and at other times no gross lesion could be seen. Not all skeletal muscles were affected [9]. Primarily, the muscles affected were those of posture and respiration, i.e., muscles performing sustained rather than strong, short-term activity [9]. Histological findings on skeletal muscles that have been investigated in the literature are given on Table 4. Muscle fibers in the muscles showing macroscopic alterations were swollen and hyaline and had lost their striations (Fig. 10a, Fig. 10b and Fig. 10c); some fibers were broken [1,12]. In some cases, examination of histological sections of muscles' pale areas showed Zencker's hyaline necrosis without any other specification [3]. The multifocal feature of the muscle alterations had to be noticed. Skeletal muscles exhibited fragmentation and swelling of individual fibers while adjacent fibers were normal [7,9,11,12]. There was no [7,9] or minimal cellular response with infiltration by macrophages or more rarely neutrophils [12,15]. Affected striated muscles showed floccular degeneration with lesions notably segmental in the myofibrils and the length of the affected segments was variable [9,15]. The earliest and mildest changes appeared to be the loss of striations and increasing eosinophilia, probably because of protein coagulation, often with pyknosis of the nuclei [9,15]. With increasing degeneration, the accumulating debris caused swelling and distension of the original fiber with granularity and flocculation of the sarcoplasm which led to sarcoplasmic condensation and discontinuity [9,15]. Some retraction bands (often in great disarray) were sometimes noticed within the sarcolemmal sheath. The sheath usually remained intact but was often locally distended causing indentation of adjacent fibers [15]. In transverse sections, swollen segments appeared up to 4 times the normal fiber diameter but nuclei generally remained peripheral. The presence, extent and severity of the changes varied between animals, muscles and samples taken within the same muscle [9,11,12,15]. Calcification of damaged fibers was minimal [9,11,12,15]. Special enzymatic reaction with myosin-ATPase permitted to certify that type I fibers only were degenerated [11]. A special coloration (Sudan III) revealed the accumulation of neutral lipids in muscular fibers of skeletal muscles and myocardium [11].



Figure 10a. Atypical myopathy-induced myodegeneration in intercostals (longitudinal section). Hematoxylin and eosin; magnification x 100. (With the permission of the "Annales de Médecine Vétérinaire" © [12]. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 10b. Atypical myopathy-induced myodegeneration in sternocephalicus muscle (longitudinal section). Hematoxylin and eosin; magnification x 100. (With the permission of the "Annales de Médecine Vétérinaire" © [12]. - To view this image in full size go to the IVIS website at www.ivis.org . -



Figure 10c. Atypical myopathy-induced myodegeneration in infraspinatus muscle (transverse section). Hematoxylin and eosin; magnification x 100. (With the permission of the "Annales de Médecine Vétérinaire" © [12]. - To view this image in full size go to the IVIS website at www.ivis.org . -

Table 4. Results of histological investigation on muscles reported in the literature								
Muscle	Reference							
	[1]	[3]	[7]	[9]	[15]	[11]	[12]	[18]
Head								
Tongue	0	0	0	-	+	0	-	0
Masseter	0	+	0	0	±	+	+	+
Neck								
No specification	0	0	0	+	+	0	0	0
Brachiocephalicus	0	0	0	0	0	0	+	+
Multifidus cervicis	0	+	0	0	0	0	0	0
Pectoralis descendens	0	0	0	0	0	+	0	0
Sternocephalicus	0	0	0	0	0	0	+	+
Other deep cervical muscles	0	+	0	0	0	0	0	0
Forelimbs								
Shoulder girdle without specification	0	0	0	+	+	0	0	0
Biceps brachii	0	0	0	0	+	0	0	0
Infraspinatus	+	+	0	0	0	0	+	0
Seratus magnus	+	+	0	0	0	0	0	0
Subscapularis	+	0	0	0	0	0	+	+
Supraspinatus	+	+	0	0	0	0	0	+
Trunk								
Lumbar region	0	0	0	0	+	0	±	±
Abdominal muscles	0	0	0	0	±	0	0	0
Diaphragm	0	0	+	+	+	+	+	+
Iliospatial	0	0	0	0	0	0	±	±
Iliopsoas	0	0	+	+	0	0	0	0
Intercostals	0	0	+	+	+	+	+	+
Latissimus dorsi	0	0	0	0	0	±	0	0
Psoas major	+	0	0	0	0	+	-	0
Hindlimbs								
Pelvic girdle without specification	0	0	0	+	0	0	0	0
Biceps femoris	+	0	0	0	0	0	0	0
Gluteus	+	0	0	0	0	0	0	0
Gracilis	0	+	0	0	0	0	0	0
Longus vastus	+	0	0	0	0	0	0	0

Muscle	Reference							
Hindlimbs								
Rectus femoris	0	+	0	0	0	0	±	0
Semimembranosus	+	0	0	0	0	0	±	0
Semitendinosus	+	0	0	0	0	±	±	0
Gluteus profundus	0	0	0	0	0	0	0	+
Legend: 0: nothing reported about this muscle or this group of muscles; -: no significant lesion; ±: mild lesions; +: severe lesions.								

Conclusion

In the literature, complete histological evaluation of main organs as well as complete histological evaluation of major postural and respiratory muscles may not be found. In addition, some of the findings enclosed in this section are issued from papers written prior to identification of atypical myopathy as a specific disorder. In further outbreaks' investigation, systematic evaluation of all vital organs and skeletal tissues should be performed. For diagnostic purpose, the muscles that should be evaluate, as a minimum to contribute to the diagnosis of atypical myopathy, include the brachiocephalicus, the sternocephalicus, the muscle of the shoulder and intercostals. When seek, degenerative lesions have been found in these muscles [1,3,7,9,12,18]. In addition, these muscles can be easily sampled on site. Because long period of recumbency may induce histological muscle degeneration that is indistinguishable from the lesions of atypical myopathy, muscle samples must be taken from places not compressed for a long time by the horse's body.

Etiological Hypotheses

D.M. Votion, V. Demoulin, E. Piat and A. Linden

A number of etiological hypotheses have been proposed some of which have been investigated. Unfortunately, results of these investigations have failed to reveal the cause of atypical myopathy but owing to these researches, it was possible to rule out some of the hypotheses. The etiologic classification of suggested causal agents is shown on Table 5. This classification includes only the causes that have been mentioned in the reviewed literature.

Toxic Products

Drugs

Monensin is an ionophore produced by the bacterium *Streptomyces cinnamonensis* (Actinomycetes). Several ionophores, that have antibiotic properties, are used widely as feed additives in poultry and livestock production. Horses are very sensitive to ionophores and accidental ingestion of these drugs may cause an acute myopathic disease [24,25]. The clinical signs, laboratory, postmortem and histological findings in atypical myopathy are, to some extent, compatible with ionophore intoxication [22]. Nevertheless, the likely cause of ionophore intoxication in horses is the accidental contamination of horse feed during its industrial production or an accidental access to ruminant foodstuffs: none of the cases reported in the literature had access to such feed [11,12,15]; in addition, testing of liver, muscles, kidneys and stomach content for ionophores yielded negative results [11,12].

Pollutants

Because of the acute nature of the syndrome, pollutants intoxication was suspected. Being potential causes of acute intoxication, nitrate, nitrite and atrazine residues were sought in water and/or soil samples of affected premises. No evidence of significant pollution with one of these products was found [11,15].

Toxins

Phytotoxins

A wide variety of toxins may be produced by plants. During the first reported outbreak [1], authors pointed out the barking of *Quercus* spp., (oak trees) by affected horses but no myopathic condition is known to be related to that practice [26]. In the second outbreak, poisoning due to *Conium maculatum* (hemlock) was considered [2] but the toxic alkaloids contained in that plant induce several clinical signs that were not present in atypical myopathy-affected horses (e.g., salivation and prolapse of the nictitating membranes [26]).

Myopathies induced by plants have been reported in America [27-33]. The best documented cases, however, are due to plants that do not occur in Europe like *Cassia occidentalis* (coffee weed or coffee senna, *Caesalpinaceae*; [27]),

Eupatorium rugosum (white snakeroot, *Compositae*, producing tremetol; [28]). Those two plants have induced myopathies in horses, while *Karwinskia humboldtiana* (coyotillo or tullidora, *Rhamnaceae*) has been shown to induce a neuropathy in goats associated with myodegeneration [29,30]. A cotton, *Gossypium ioxiolena* (*Malvaceae*) and four types of alkaloid producing *Papilionaceae* may also be responsible to some degree for a myopathy syndrome [31-33]. The above-mentioned *Papilionaceae* include a plant found in America (*Thermopsis montana* from the Rocky Mountains) and plants from three genera that can be found in Europe [1. *Laburnum anagyroides* (i.e., *Cytisus laburnum*, golden chain or golden rain), 2. *Cytisus scoparius* (i.e., *Sarothamnus* sc., broom), and 3. various lupins (i.e., *Lupinus* div. spp.)]. From those plants, only the broom is common enough to have been accessible to some of the dead horses. However, it is restricted to acid soils and its well known toxicity has always been considered mild.

Some other common plants known to be toxic for horses (i.e., *Ranunculus acris* and *R. repens*, the common buttercups and *Glechoma hederacea*, a ground ivy widely found in shaded grounds) have been found by Brandt and collaborators [11] but signs of poisoning with these plants are not the ones of atypical myopathy [34]. Cardiac dysfunction may result from ingestion of *Vicia* spp., (common vetch [35]) which were found on some premises [11]. Ingestion of wilted or dried leaves of *Acer rubrum* (red maple) may result in a fatal syndrome accompanied by the emission of colored urine. However, the clinical signs result from a hemolytic process which has no myopathic component [36,37].

Specific climatic conditions might be a prerequisite for a plant to exert its toxicity. For example, these may render the plant more palatable, they may make the plant more accessible for eating (e.g., winds bringing vegetation to the ground), and/or they may trigger metabolic changes in the plant inducing its toxicity.

Mycotoxins

Fungi produce an incredible diversity of metabolites, some of them toxic to animals [38]. The seasonal occurrence of atypical myopathy and its association with particular climatic conditions may suggest a mycotoxin as the cause of atypical myopathy. Indeed, mycotoxin production by some molds may be enhanced or induced in response to environmental factors such as humid conditions and/or an atypical temperature [39].

Fusarium fungi were found in some grass samples collected on affected premises by Brandt and collaborators [11]. These molds may produce fumonisins which are toxins causing mild to fatal diseases in animals [40]. Horses appear to be particularly sensitive to fumonisins which induce in them equine leukoencephalomalacia [41]. However, the *Fusarium* spp., may also produce mycotoxins of the trichothecenes family which have been suspected as a possible cause of atypical myopathy [7]. Trichothecene mycotoxins may also be produced by *Trichoderma* fungi that were consistently isolated from grass and wood from the fields grazed by affected horses in one study [7] but not in a latter one [11]. Given their high toxicity and wide distribution among several genera of molds, trichothecenes should continue to be investigated.

In the collected samples, Brandt and collaborators [11] found *Acremonium lolii*, a fungal endophyte known to produce toxins called lolitrems. Poisoning with lolitrem B induces severe neurological signs, producing the ryegrass staggers syndrome but again, muscles are not involved in this disease [42]. In addition, analysis of samples did not demonstrate the presence of lolitrem B [11].

Ingestion of macroscopic fungi may exceptionally be toxic for muscles. In European countries, a new myopathy syndrome affecting humans has recently been attributed to fungi of the group of *Tricholoma equestre* (*Tricholoma flavovirens*, the knightly tricholoma; Fig. 11) which was considered edible up to the first intoxication outbreak [43,44]. Repeated consumption of this wild mushroom may cause fatal rhabdomyolysis. In Japan, another mushroom, *Russula subnigricans*, has also been recently reported as being myotoxic [45]. While those macroscopic fungi may give some indications in the search for a myotoxic molecule, an implication of macrofungi in the horse poisoning does not seem very probable.



Figure 11. *Tricholoma flavovirens*. Kindly provided by Fred Stevens ©. - To view this image in full size go to the IVIS website at www.ivis.org . -

Bacterial Toxins

Delguste and collaborators [12] underlined the possibility of *Clostridium* spp., involvement in atypical myopathy. Clostridia are common soil and enteric bacteria, therefore their identification in ground samples and/or digestive tract content of affected horses would be of little value in demonstrating their role in pathogenesis of atypical myopathy. In addition, dormant clostridial spores are commonly present in healthy equine skeletal muscle [46], therefore diagnosis of clostridial infection would require demonstration of clostridial toxins. Because horses are extremely sensitive to botulinum toxins, it might be of interest to search for the presence of the different toxin types that may be produced by *Clostridium botulinum*. Unfortunately, there is no available test for routine diagnosis of all the known toxins. Non-traumatic *Clostridium septicum* myonecrosis is quite unusual but has been sporadically reported in the human medicine literature [47]. Once again to demonstrate involvement of *Clostridium septicum* in atypical myopathy, the detection of its specific alpha toxin, which is myotoxic, would be of greater value than the detection of the bacterium itself.

Ionophores intoxication via feed additives has been excluded [11,12,15], however, it may be hypothesized that *Streptomyces* spp., fermentation in the grazing milieu might be a source of natural exposure to ionophores. Unfortunately,

testing for ionophores is difficult because toxin levels in blood and/or tissue are frequently too low to be traceable [24].

Viruses

No evidence of a recent infection with equine adenoviruses, bornavirus, influenza virus, herpesviruses, rhinoviruses and the swine picornavirus has been found [11,12,15]. These viruses have been to some extent involved in acute death syndromes and/or myopathic disorders and concerning the swine picornavirus, in cardiomyopathy (in the hypothesis of a viral transmission from wild boars to horses [12]).

Hormonal Dysfunction

Hypothyroidism is a rare but reported primary cause of rhabdomyolysis in humans and dogs [48-51]. In dogs suffering from primary hypothyroidism, muscle biopsies demonstrated atrophy of type II and hypertrophy of type I muscle fibers which suggested a metabolic defect in fast-twitch muscle fibers [48]. In horses, thyroid dysfunction was suspected as a contributory factor to poor racing performances and myopathic disorders [21]. It is, however, unlikely that hypothyroidism plays a major part of the pathophysiology of atypical myopathy. Whether it may be a predisposal factor remains undetermined.

Table 5. Classification according to etiological hypotheses		
Potential	Potential causal agents	Results of investigation when the agent was sought
Toxics		
Drugs	Monensin	Negative
Pollutants	Atrazine residues	No significant pollution levels
	Nitrate and/or nitrite	No significant pollution levels
Toxins		
Phytotoxins	<i>Cassia occidentalis</i>	Plant not found
	<i>Conium maculatum</i>	Plant found but toxic effects do not match entirely clinical signs of atypical myopathy
	<i>Cytisus</i>	Plant not found
	<i>Eupatorium rugosum</i>	Plant not found
	<i>Gossypium</i>	Plant not found
	<i>Ixioloena</i>	Plant not found
	<i>Karwinskia</i>	Plant not found
	<i>Lupinus</i>	Plant not found
	<i>Quercus</i> spp.	Plant found but no reported myopathic toxicity
	Red Mapple	Uncommon plant in European pastures; no reported myopathic toxicity
	<i>Vicia</i>	Plant found; potential cardiac toxicity
Mycotoxins	<i>Acremonium lolii</i>	Fungal endophyte found but not its toxin
	<i>Fusarium</i> spp.	Fungi found
	<i>Trichoderma</i>	Not consistently found
Bacterial toxins	Actynobacteria <i>St. cinnamomensis</i>	Toxin not found (i.e., monensin)
	Clostridia <i>Cl. botulinum</i> <i>Cl. septicum</i>	Inconclusive tests

Potential	Potential causal agents	Results of investigation when the agent was sought
Toxins		
Viruses	Equine adenoviruses Bornavirus Equine influenza virus Equine herpesviruses Equine rhinoviruses Swine picornavirus	No evidence of recent infection
Hormonal dysfunction	Hypothyroidism	Negative
Nutritional deficiency	Vitamin E/selenium deficiency	Equivocal

Nutritional Myopathy

Nutritional myopathy, also called nutritional myodegeneration, white muscle disease or improperly, nutritional muscular dystrophy, is a primary cardiac and/or skeletal myodegeneration caused by a dietary deficiency in selenium and/or vitamin E (i.e., alpha-tocopherol). Although the pathophysiology of this syndrome is still unclear, it is thought that deficiency of either one or both compounds results in insufficient protection of cell membranes against reactive oxygen species which in turn would lead to cell membrane and muscle cells injury [52].

In horses, this syndrome can be identified clinically in two forms [53]. The first is a frequently fatal acute to peracute disease which mimics atypical myopathy in many aspects. The second is a less acute form which causes profound muscular weakness, sometimes associated with dysphagia. The main differences between atypical and nutritional myopathy are the affected horses' age range and the seasonality of the diseases. Classically, nutritional myopathy affects young, rapidly growing foals, particularly those born to dams fed selenium deficient diets during gestation [54], but the disease has also been exceptionally reported in adult horses [55]. Because nutritional myopathy occurs predominantly in foals younger than two months old, the condition has a seasonal occurrence linked to the foaling season (i.e., in the northern hemisphere, from late winter until the end of spring [53]). Regardless of these differences, the peracute form of the disease is almost indistinguishable from atypical myopathy; see Table 6. Clinical signs look a lot like those of atypical myopathy. In addition, clinical signs of nutritional myopathy may also be triggered by external factors such as cold weather. Sudden exercise after a period of confinement is another well-known precipitating factor in nutritional myopathy whereas, in atypical myopathy there is still a doubt concerning the role of unusual exercise [3,18]. Whatever the initial pathological process, muscle cells suffering acute damage tend to go through a common final pathway of muscle fiber degeneration [56]. In addition, skeletal and cardiac muscle discoloration as well as selective destruction of type I skeletal muscle fibers have been found in both diseases [11,57].

Table 6. Features shared by both atypical and nutritional myopathy	
Characteristics of atypical myopathy	Similarities with nutritional myopathy (peracute form)
History	
Pastured horses; grass being the main part of alimentation	± : may also affect stabled horses with a vitamin E and/or selenium deficient alimentation
Foals, yearlings and adult horses	±: mainly foals under two months old
Seasonal occurrence: fall & winter > spring	±: predominantly late winter and spring
Horses in good bodily condition	X
Clinical series; occasionally, isolated case	±: isolated case; occasionally, concurrent cases
Sudden onset of clinical signs	X
Signs may be triggered by external factors	X

Characteristics of atypical myopathy	Similarities with nutritional myopathy (peracute form)
Clinical signs	
Muscle weakness and stiffness	X
Sudation and muscle tremors	X
Recumbency	X
Tachypnea and dyspnea	X
Tachycardia	X
Hypothermia or normal temperature	±: occasional hyperthermia would result from struggling and in some cases, from aspiration pneumonia
Rapid degradation of clinical signs	X
Animal not anorexic	X
Possible dysphagia	X (frequently encountered in the less acute form)
Myoglobinuria	X
No evident signs of colic	X
High mortality rate; quick death	X
Not responsive to vitamin E/selenium treatment	X
Laboratory data	
Marked increase of muscle enzymes activity	X
Occasionally, increased liver enzymes activity	X
Hypocalcemia	X
Postmortem examination	
Postural, respiratory and cardiac muscle discoloration	X
Occasionally, no significant gross lesions	X
Histological findings	
Non inflammatory muscle degenerative	X
Necrosis of type I fibers	X

A diagnosis of nutritional myopathy is usually based on the observation of typical but non pathognomonic clinical signs, marked elevation in muscle enzymes activity, deficient levels of selenium and/or vitamin E (i.e., in foals, dams and/or diets) and at postmortem, observation of non inflammatory skeletal and/or cardiac muscles degeneration. In non recumbent cases, a clinical response to vitamin E/selenium administration may also contribute to the diagnosis but in highly acute cases, a clinical response is not expected [58]. Although vitamin E and more particularly selenium deficiencies are linked to nutritional myopathy, not all deficient animals develop clinical myopathy [59]. In addition, selenium and vitamin E supplementation does not consistently protect against the disease occurring in foals born from deficient mares [60].

Selenium is an essential component of glutathione peroxidase (GSH-Px), an enzyme formed in the red cells during erythropoiesis. Assessment of selenium status can be approached by measuring both GSH-Px activity in whole blood and selenium levels in sera. Several seleno-proteins which participate to various redox reactions have been recently identified [61] and might be of interest to better understand the pathophysiology of nutritional myopathy in horses.

Selenium deficiency as a primary cause of atypical myopathy has been challenged by the following observations:

1. While blood selenium, as measured by GSH-Px activity and/or seric levels was found to be low or within the normal range in atypical myopathy-affected horses [4,7,9,11,15], selenium status of unaffected co-grazing horses was also frequently deficient [4,7,15]. However, this finding (i.e., a low selenium level in healthy companion of diseased animal) is not uncommon in nutritional myopathy [62];
2. Atypical myopathy occurred in a few horses 48 hours following the preventive administration of vitamin E plus selenium [9,12];
3. Treatment of atypical myopathy-affected horses with vitamin E/selenium administration was often unsuccessful [3,9,11,12];
4. Typical bilateral muscle discolorations and histological changes in cardiac muscle frequently seen in nutritional myopathy were not found in several clinical series of atypical myopathy [9,12]. However, muscle discolorations and/or cardiac muscle alterations have been found in other cases of atypical myopathy [1,12,15].

The antioxidant status of an animal could be very important in determining its susceptibility to the yet unknown atypical myopathy etiological agent. For example, selenium and other compounds with antioxidant properties have been showed to exert a role in the prevention of several mycotoxicoses [63] such as those induced by two major toxins of the *Fusarium* spp., (i.e., the highly toxic T-2 toxin, a toxin of the trichothecene group [64]; and, fumosin B1 [65] that induces leukoencephalomalacia in horses). Determining the antioxidant status of future atypical myopathy cases might be of interest towards the understanding of the pathophysiology of this syndrome.

Conclusion

So far, the cause of atypical myopathy remains unknown. Most probably, the condition is induced by an ingested or enterically produced toxin (the most probable being a bacterial or fungal toxin). In the light of the reviewed studies, drugs or pollutants intoxication, viral infection and thyroid dysfunction are the least likely causes. Whether nutritional deficiencies, such as selenium deficit, play a role in the pathogenesis of atypical myopathy remains to be investigated.

Epidemiology

C. Delguste, E. Thiry, E. Piat, A. Linden and D.M. Votion

This section focuses on the need to apply epidemiologic methods to the investigation of atypical myopathy outbreaks [66]. Occurrence of the clinical syndrome in a horse implies that appropriate circumstances to the onset of the condition were present in the host and/or in its environment. Epidemiological investigation would contribute to a straightforward identification of those circumstances, thus defining the real importance of suggested risk (e.g., climatic conditions, stress and exercise) and/or causal factors. In addition, collection of additional and more precise clinical data would be of great value to refine the syndrome description and definition. Finally, detailed knowledge of the epidemiology of atypical myopathy is required to raise hypotheses concerning its etiology as well as to be able to suggest potential preventive measures.

Outbreak investigation will initially require two phases [67]: a descriptive and an analytic phase. Descriptive epidemiology will enable a more accurate description of the ecology, history and clinical signs of atypical myopathy and can also suggest potential risk factors. On the other hand, analytic epidemiology will contribute to the determination of factors (i.e., risk factors) that are associated with an increased or decreased likelihood of contracting atypical myopathy. From results of these epidemiological approaches, an intervention phase that aimed at preventing further cases may potentially be drawn.

Descriptive Epidemiology

By collecting patterns in temporal, geographical and host distributions as well as detailed description of history and clinical signs, a more precise description of atypical myopathy may be obtained. This is the first step required to establish an accurate case and non-case definition. To that purpose, epidemiological and clinical questionnaires are proposed in Annex I (PDF format - 122Kb) and Annex II (PDF format - 129Kb), respectively. In the epidemiological questionnaire, data related to history, pasture and climatic conditions are requested. In the clinical questionnaire, results of a primary physical clinical examination and queries relative to specific clinical signs or particular behaviors are asked for. In addition, a few complementary examinations and laboratory tests are suggested.

If information relative to the horses clinically affected by atypical myopathy is of paramount importance, information relative to their co-grazing unaffected companions is perhaps even more interesting. Investigating the difference(s) between affected and unaffected horses (i.e., cases and non-cases) may enable the suggestion of potential risk factors or may even contribute to the discovery of the causal agent. Therefore, the epidemiological questionnaire should also be applied to co-grazing horses as well as a clinical questionnaire proposed in Annex III (PDF format - 102Kb).

Analytic Epidemiology

The main objective of this phase is the determination of risk factors. These factors might be related to the host (e.g., host

susceptibility due to age, sex or breed), timing (e.g., season), location (e.g., local geological or ecological factors) and other miscellaneous features (e.g., type of feed, climatic conditions, horses' use). This analytic phase may contribute to drawing hypotheses or even ruling some of them out (e.g., concerning the source of contamination).

Intervention Phase

Assuming that atypical myopathy is a multifactorial condition, analytic epidemiology will aim at classifying potential component causes as: (1) predisposing factors which increase the level of susceptibility (e.g., age and sex); (2) enabling factors which facilitate manifestation of the syndrome (e.g., housing and nutrition) and, (3) precipitating factors (e.g., specific climatic conditions). From the determination of these factors, preventive measures might be suggested even if the primary causal agent remains unidentified. Because of the acute nature of the condition and the rapid progression of severe clinical signs, prevention is more important than treatment. Up to now, the unique valuable preventive measure that may be advised is to bring horses in from pasture in the beginning of fall and not to turn them out before the end of spring!

International Atypical Myopathy Alert Site

Atypical myopathy is a sporadic, perhaps multifactorial, myopathy that cannot be, at this time, reproduced experimentally. Progress in understanding the pathophysiology of the syndrome relies essentially on outbreaks investigation from both clinical and epidemiological aspects. As mentioned earlier (see "Introduction"), no manifestation of atypical myopathy may be encountered for several years in a country previously severely touched by the syndrome. On the other hand, an unaffected country may suddenly face a large number of cases. The use of standardized methods for epidemiological data collection by clinicians involved with atypical myopathy outbreaks, might provide a means for comparing different studies. In addition, the inventory of confirmed and suspected cases of atypical myopathy on a reference website would contribute to establishing the incidence of the condition throughout the world.

Clinicians are encouraged to use the submission forms to report new cases and email these to the International Atypical Myopathy Alert Site (dominique.votion@ulg.ac.be). This will hopefully contribute to connecting people working occasionally or permanently on this syndrome, thus favoring scientific collaboration.

Submission Forms (click on the appropriate document format to download)

Epidemiology Questionnaire	PDF in English	Word in English	PDF in French	Word in French
Clinical Questionnaire (suspected Atypical Myopathy)	PDF in English	Word in English	PDF in French	Word in French
Clinical Questionnaire for Pasture Companions (non-affected Horses)	PDF in English	Word in English	PDF in French	Word in French
Necropsy Questionnaire (suspected Atypical Myopathy)	-	-	PDF in French	Word in French
Case Record (Atypical myopathy: listing of suspected cases)	PDF in English	Excell in English	PDF in French	Excell in French

Acknowledgements

The authors gratefully acknowledge the Ministry of Agriculture and Rurality of Belgium (Region wallonne) for their funding support. We would also like to thank Eva Orban from the Szent Istvan University of Hungary, for looking in the Veterinary Science Library archives in search of old veterinary books written by Hutyrá and collaborators and Fred Stevens for providing the *Tricholoma flavovirens* picture.

References

1. Bowen JN, Craig JF. Myoglobinuria in horses. *Vet Rec* 1942; 35:354.
2. Pope DC, Heslop CH. An outbreak of myoglobinuria in light horses. *Can Vet J* 1960; 1:171-174.
3. Tritschler LG, Miles D. An outbreak of myoglobinuria. *Vet Med Small Anim Clin* 1966; 61:649-651.
4. Carthé D, Ansay M, Lomba F, et al. Myoglobinurie chez des poulains de demi-sang de sept mois. *Ann Méd Vét* 1976; 120:325-331.
5. Liégeois F. Muscles: myopathie myoglobulinurique enzootique. In: Duculot J, ed. *Traité de pathologie médicale des animaux domestiques*. Gembloux: Librairie agricole de la maison rustique, 1933; 847-850.
6. Hutyrá F, Marek J, Manninger R. Enzootic myoglobinuria of horses (Myoglobinuria Enzootica Equorum). In: Greig JR,

Mohler JR, Eichhorn A, eds. Special pathology and therapeutics of the diseases of domestic animals (5th edn; Vol III). London: Baillière, Tindall and Cox, 1946; 144-147.

7. Anonymous. Atypical myoglobinuria: a new disease in horses? *Vet Rec* 1985; 116:86-87.
8. Linklater KA. Myopathy in horses and ponies. *Vet Rec* 1984; 115:666.
9. Hosie BD, Gould PW, Hunter AR, et al. Acute myopathy in horses at grass in east and south east Scotland. *Vet Rec* 1986; 119:444-449.
10. Harris P, Whitwell K. Atypical myoglobinuria alert. *Vet Rec* 1990; 127:603.
11. Brandt K, Hinrichs U, Glitz F, et al. Atypische Myoglobinurie der Weidepferde. *Pferdeheilkunde* 1997; 13:27-34.
12. Delguste C, Cassart D, Baise E, et al. Myopathies atypiques chez les chevaux au pré: une série de cas en Belgique. *Ann Méd Vét* 2002; 146:231-243.
13. Moussu C, Saison A, Bermann F, et al. La myoglobinurie atypique des équidés : une nouvelle maladie ? In: Proceedings of the "Journées scientifiques de l'AESA - AEEMA", 2003; 16-17.
14. Irwin CFP, Pulsford MF. Enzootic myoglobinuria in a horse. *Aust Vet J* 1951; 27:101-102.
15. Whitwell KE, Harris P, Farrington PG. Atypical myoglobinuria: an acute myopathy in grazing horses. *Equine Vet J* 1988; 20:357-363.
16. Robinson HC. Atypical myoglobinuria. *Vet Rec* 1991; 128:44.
17. Hillam RA. Atypical myoglobinuria. *Vet Rec.* 1991; 128:166.
18. Votion DM, Delguste C, Baise E, et al. Diagnostic différentiel en cas de présomption de myopathie atypique des équidés: illustration au travers de cas référés à la Faculté de Médecine Vétérinaire de l'Université de Liège au cours du printemps 2003. *Ann Méd Vét* 2003; 147:183-193.
19. Votion DM, Delguste C, Amory H, et al. La myopathie atypique des équidés : particularités cliniques, examens complémentaires et hypothèses étiologiques. In: Proceedings of "Journée AVEF", 2003; 244-254.
20. Perkins G, Valberg SJ, Madigan JM, et al. Electrolyte disturbances in foals with severe rhabdomyolysis. *J Vet Intern Med*, 1998; 12:173-177.
21. Waldron-Mease E. Hypothyroidism and myopathy in racing thoroughbreds and standardbreds. *J Equine Med Surg* 1979; 3:124-128.
22. Harris PA. Musculoskeletal disease. In: Reed SM, Bayly WM, eds. *Equine internal medicine*. Philadelphia: WB Saunders Co, 1998; 371-426.
23. Volfinger L, Lassourd V, Michaux JM, et al. Kinetic evaluation of muscle damage during exercise by calculation of amount of creatine kinase released. *Am J Physiol*, 1994; 266:R434-441.
24. Novilla MN. The veterinary importance of the toxic syndrome induced by ionophores. *Vet Hum Toxicol* 1992; 34:66-70.
25. Harris PA. Differential diagnosis of an acute episode of a primary myopathy out at pasture. *Equine Vet Educ* 1996; 8:272-276.
26. Knight AP, Walter RG. Plants causing sudden death. In: Knight AP, Walter RG, eds. *A guide to plant poisoning of animals in North America*. Ithaca: International Veterinary Information Service.
27. Martin BW, Terry MK, Bridges CH, et al. Toxicity of *Cassia occidentalis* in the horse. *Vet Hum Toxicol* 1981; 23:416-417.
28. Olson CT, Keller WC, Gerken DF, et al. Suspected tremetol poisoning in horses. *J Am Vet Med Assoc* 1984; 185:1001-1003.
29. Charlton KM, Claborn LD, Pierce KR. A neuropathy in goats caused by experimental coyotillo (*Karwinskia humboldtiana*) poisoning: clinical and neurophysiologic studies. *Am J Vet Res* 1971; 32:1381-1389.
30. Knight AP, Walter RG. Plants affecting the nervous system. In: Knight AP, Walter RG, eds. *A guide to plant poisoning of animals in North America*. Ithaca: International Veterinary Information Service.

31. Knight AP. Plant poisoning of horses. In: Lewis LD ed. Feeding and care of the horse (2nd edn). Williams & Wilkins: Media 1996, 300-345.
32. Radostits OM, Gay CC, Blood DC, et al. Diseases caused by toxins in plants, fungi, cyanophytes, clavibacteria, and venoms in ticks and vertebrate animals. In : Radostits OM, Gay CC, Blood DC, et al, eds. Veterinary medicine: a textbook of the diseases of cattle, sheep, pigs, goats and horses (9th edn). London: WB Saunders Co, 2000, 1631-1708.
33. Bruneton J. Plantes toxiques: végétaux dangereux pour l'homme et les animaux. In: Lavoisier, ed. Technique & Documentation (2nd edn). Paris : Ed Médicales Internationales, 2001, 564p.
34. Knight AP, Walter RG. Plants affecting the digestive system. In: Knight AP, Walter RG, eds. A guide to plant poisoning of animals in North America. Ithaca: International Veterinary Information Service.
35. Radostits OM, Gay CC, Blood DC, et al. Diseases of the cardiovascular system. In : Radostits OM, Gay CC, Blood DC, et al, eds. Veterinary medicine: a textbook of the diseases of cattle, sheep, pigs, goats and horses (9th edn). London: WB Saunders Co, 2000, 361-398.
36. Corriher CA, Parviainen AKJ, Gibbons DS, et al. Equine red maple leaf toxicosis. *Comp Cont Edu Pract* 1999; 21:74-80.
37. Knight AP, Walter RG. Plants affecting the blood. In: Knight AP, Walter RG, eds. A guide to plant poisoning of animals in North America. Ithaca: International Veterinary Information Service.
38. Moss MO. Mycotoxins. *Mycol Res* 1996; 100:513-523.
39. Osweiler GD. Mycotoxins. *Vet Clin North Am Equine Pract* 2001; 17:547-566.
40. Bucci TJ, Howard PC, Tolleson WH, et al. Renal effects of fumonisin mycotoxins in animals. *Toxicol Pathol* 1998; 26:160-164.
41. Uhlinger C. Leukoencephalomalacia. *Vet Clin North Am Equine Pract* 1997; 13:13-20.
42. Cheeke PR. Endogenous toxins and mycotoxins in forage grasses and their effects on livestock. *J Anim Sci* 1995; 73:909-918.
43. Bedry R, Baudrimont I, Deffieux G, et al. Wild -mushroom intoxication as a cause of rhabdomyolysis. *N Engl J Med* 2001; 345:798-802.
44. Chodorowski Z, Waldman W, Sein Anand J. Acute poisoning with *Tricholoma equestre*. *Przegl Lek* 2002; 59:386-387.
45. Lee PT, Wu ML, Tsai WJ, et al. Rhabdomyolysis: an unusual feature with mushroom poisoning. *Am J Kidney Dis* 2001; 38:E17.
46. Vengust M, Arroyo LG, Weese JS, et al. Preliminary evidence for dormant clostridial spores in equine skeletal muscle. *Equine Vet J* 2003; 35:514-516.
47. Abella BS, Kuchinic P, Hiraoka T, et al. Atraumatic Clostridial myonecrosis: case report and literature review. *J Emerg Med* 2003; 24:401 -405.
48. Braund KG, Dillon AR, August JR, et al. Hypothyroid myopathy in two dogs. *Vet Pathol* 1981; 18:589-598.
49. Barahona MJ, Mauri A, Sucunza N, et al. Hypothyroidism as a cause of rhabdomyolysis. *Endocr J* 2002; 49:621-623.
50. Braund KG. Myopathic disorders. In: Braund KG, ed. Clinical neurology in small animals - Localization, diagnosis and treatment. Ithaca: International Veterinary Information Service.
51. Kisakol G, Tunc R, Kaya A. Rhabdomyolysis in a patient with hypothyroidism. *Endocr J* 2003; 50:221-223.
52. Saito Y, Yoshida Y, Akazawa T, et al. Cell death caused by selenium deficiency and protective effect of antioxidants. *J Biol Chem* 2003; 278:39428-39434.
53. Löfstedt J. White muscle disease of foals. *Vet Clin North Am Equine Pract* 1997; 13:169-185.
54. Higuchi T, Ichijo S, Osame S, et al. Studies on serum selenium and tocopherol in white muscle disease of foal. *Nippon Juigaku Zasshi* 1989; 51:52-59.
55. Owen RR, Moore JN, Hopkins JB, et al. Dystrophic myodegeneration in adult horses. *J Am Vet Med Assoc* 1977; 171:343-349.

56. Knochel JP. Mechanisms of rhabdomyolysis. *Curr Opin Rheumatol* 1993; 5:725-731.
57. Hulland TJ. Muscles and tendons. In: Jubb KVF., Kennedy PC, Palmer N, eds. *Pathology of domestic animals* (3rd edn). Orlando: Academic Press, 1985; 139-199.
58. Hamir AN. White muscle disease of a foal. *Aust Vet J* 1982; 59:57-58.
59. Caple IW, Edwards SJ, Forsyth WM, et al. Blood glutathione peroxidase activity in horses in relation to muscular dystrophy and selenium nutrition. *Aust Vet J* 1978; 54:57-60.
60. Wilson TM, Morrison HA, Palmer NC, et al. Myodegeneration and suspected selenium/vitamin E deficiency in horses. *J Am Vet Med Assoc* 1976; 169:213-217.
61. Holben DH, Smith AM. The diverse role of selenium within selenoproteins: a review. *J Am Diet Assoc* 1999; 99:836-843.
62. Roneus B. Glutathione peroxidase and selenium in the blood of healthy horses and foals affected by muscular dystrophy. *Nord Vet Med* 1982; 34:350-353.
63. Atroshi F, Rizzo A, Westermarck T, et al. Antioxidant nutrients and mycotoxins. *Toxicology* 2002; 180:151-167.
64. Keshavarz SA, Memarbashi A, Balali M. Preventive effect of selenium on T-2 toxin membrane toxicity. *Adv Exp Med Biol* 2001; 500:463-466.
65. Atroshi F, Rizzo A, Biese I, et al. Fumonisin B1-induced DNA damage in rat liver and spleen: effects of pre-treatment with coenzyme Q10, L-carnitine, alpha-tocopherol and selenium. *Pharmacol Res* 1999; 40:459-467.
66. Cohen ND. The John Hickman memorial lecture: colic by numbers. In: Marr CM, Jeffcott LB, Mair TS, Muir WW, eds. *Equine Veterinary Journal special issue: evidence based medicine*. *Equine Vet J* 2003; 35:343-349.
67. Smith RD. Epidemiology for the equine practitioner. *Vet Clin North Am Equine Pract* 2001; 17:419-432.

All rights reserved. This document is available on-line at www.ivis.org. Document No. R0101.1106

