Animal Science Papers and Reports vol. 37 (2019) no. 3, 233-242
Institute of Genetics and Animal Breeding, Jastrzębiec, Poland

Equine atypical myopathy – a review*

Olga Witkowska-Piłaszewicz[1,2], Ilona Kaszak[3], Magdalena Żmigrodzka[2], Anna Winnicka[2], Mariusz Sacharczuk[4], Jarosław Szczepaniak[5], Anna Cywińska[2]**

[1] Department of Internal Diseases and Veterinary Diagnostics, Faculty of Veterinary Medicine and Animal Science, Poznan University of Life Sciences, Wołyńska 33, 60-616 Poznań, Poland

[2] Department of Pathology and Veterinary Diagnostics, Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Nowoursynowska 166, 02-787 Warsaw, Poland

[3] Department of Small Animal Diseases with Clinic, Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Nowoursynowska 166, 02-787 Warsaw, Poland

[4] Laboratory of Neurogenomics, Institute of Genetics and Animal Breeding, Jastrzębiec, Postępu 36A, 05-522 Magdalenka, Poland

[5] Department of Animal Nutrition and Biotechnology, Faculty of Animal Science, Warsaw University of Life Sciences

(Accepted March, 2019)

Equine atypical myopathy (EAM) is an acute, severe rhabdomyolysis associated with ingestion of hypoglicyn A contained in seeds and seedlings of Sycamore maple (*Acer pseudoplatanus*). An increasing number of outbreaks has been reported in recent years, including some from countries where the disease has not been previously diagnosed. EAM occurs predominantly during the autumn and less often in the spring. Treatment plans can be extrapolated from the described clinical signs and metabolic problems, but they remain limited to supportive care. Since treatment is still unsuccessful in the majority of cases, the main emphasis is currently still on prevention. In this review, clinical and other details of EAM are analysed.

KEY WORDS: hypoglicyn A / muscle disorders / myoglobinuria / rhabdomyolysis

---

*The study was supported by a grant from National Science Centre, grant number 2017/25/N/NZ6/02750.
**olga.witkowska.pilaszewicz@gmail.com

Muscle disorders, which are a common cause of disability in affected horses, constitute a large variety of both acquired and hereditary disorders that can affect muscle structure, metabolism or the function of the muscle channel. Equine atypical myopathy (EAM) also known as a seasonal pasture myopathy, or acquired equine multiple acyl-CoA dehydrogenase deficiency, is an acquired muscle disease affecting grazing horses. It has been shown that horses kept on overgrazed pasture with a large quantity of dead leaves and dead wood and/or without an adequate hay or other supplementary feedstuffs are at particular risk. It occurs mainly during autumn, sometimes in spring months, frequently after a period of wet and windy or cold weather.

EAM is an acute disorder accompanied by extensive rhabdomyolysis resulting in muscular weakness, stiffness, recumbency, myoglobinuria and at least 75% of cases lead to death within 72 h [van Galen *et al.* 2012]. EAM can affect individual horses or several horses within the same group. All horses are potentially susceptible to EAM, although youngsters and horses above the age of 20 have been found to be at greater risk. This syndrome is not connected with any physical exertion for the clinical signs to manifest themselves, unlike myopathies caused by strenuous exercise. The number of cases reported worldwide in recent years is increasing.

Epidemiology

Equine atypical myopathy was first recognized in grazing horses in 1939 in East Scotland and first reported in the literature in 1942 [Bowen *et al*. 1942]. In 1995 the first major outbreak occurred in Germany, raised awareness of the condition worldwide because of 111 horses death, which presented clinical signs typical for rhabdomyolysis [Brandt *et al.* 1997]. There are number of reports describing the disorder from various European countries. Now the disease has been recognized in Belgium, Denmark, France, Germany, Ireland, United Kingdom, Latvia, Luxembourg, Spain, Switzerland, and The Netherlands but also in Austria, Italy, Norway, and Sweden [Palencia *et al*. 2007, van Galen *et al*. 2012, McKenzie *et al*. 2016, Votion *et al.* 2007b, unpublished data from the Atypical Myopathy Alert Group; AMAG]. Also, EAM occurred in Australia, Canada and the USA [Votion *et al.* 2009]. The newest outbreaks have been recorded in Czech Republic [Karlíková *et al.* 2016]. To the authors' knowledge, no cases have previously been reported in Poland but it does not mean that there is no risk of EAM outbreak.

The investigation of the cause

From the beginning environmental toxins were considered as potential causative agents for EAM. Sparse pastures with an accumulation of dead leaves, dead wood and trees in/ or around the pasture and frequently contained wet areas are the main cause of this illness. The possibility of viral or bacterial infection was suspected. However, participation of viruses such as: equine influenza virus, rhinopneumonitis virus,

rhinoviruses, adenoviruses [Whitwell *et al*. 1988], Borna disease virus or herpesvirus infection [Brandt *et al.* 1997] in pathogenesis was excluded. The participation of bacteria/fungus and their toxins, e.g. *Clostridium sordellii* or mycotoxins *Rystisma acerinum*, which lead to dysfunction of the mitochondrial metabolism in horses, were subsequently investigated but the results were inconsistent [Valberg *et al.* 2013, Gerber *et al.* 2006].

Nutritional myopathy (e.g. acute oxidative skeletal muscle) was also proposed as a contributing factor but low dietary selenium has been excluded. Most of reported cases of EAM have adequate serum, kidney and/or liver concentrations of a tocopherol [Whitwell *et al.* 1988].

More precise studies, such as tissues histopathological examination showed the possible cause of the disease. Morphopathological examination of EAM cases showed an acute and degenerative process as a result of intracellular accumulation of lipids in the slow oxidative type I muscle fibres. In humans with multiple acyl-CoA dehydrogenase deficiency (MADD) there are mutations in the electron transport flavoprotein (ETF) system, which are essential for fatty acid β-oxidation and metabolism of branched amino acids, glutarate and choline [Watmough *et al*. 2010]. This indicated that the disease shared multiple similarities with an acquired MADD condition called Jamaican vomiting sickness which is triggered by the ingestion of ackee fruit (*Blighia sapida*) that contains hypoglicyn A [Katibi *et al.* 2015]. The presence of plants which contains hypoglicyn A is a common feature in outbreaks of EAM. Species vary considerably between countries. In the USA, the Box elder (*Acer negundo*) has recently been linked to cases of EAMIn Europe it is the Sycamore maple (*Acer pseudoplatanus*) (Fig. 1, 2, 3). It should be mentioned that many environmental factors can have an influence on the level of hypoglicyn A in seeds, e.g. species such as the Norway maple (*Acer platanoides*) (Fig. 4, 5, 6) and the Field maple (*Acer campestre*) does not seem to contain hypoglicyn A [Votion *et al*. 2014, Unger *et al.* 2014, Baise *et al.* 2016].

Fig. 1. The sycamore maple (*Acer pseudoplatanus*) leaf has a significantly less jagged edge and smaller notches (photo © Robert Sadowski www.drzewapolski.pl)

Fig 2. In autumn sycamore leaves never turn red. They usually go a blotchy green-yellow(photo: © Robert Sadowski www.drzewapolski.pl).

Fig. 3. The sycamore seeds (*Acer pseudoplatanus*). Opening angle is smaller (about 90%) (photo: © Robert Sadowski www.drzewapolski.pl).

Fig. 4. The Norway maple (*Acer platanoides*) leaf has a glossier surface, the lobes each bear one to three side teeth, and an otherwise smooth margin (photo © Robert Sadowski www.drzewapolski.pl).

Fig. 5. In autumn Norway Maple leaves are some of the first to change colour, turning a blazing scarlet or yellow (photo: © Robert Sadowski www.drzewapolski.pl).

Fig. 6. The Norway Maple seeds are disc-shaped, strongly flattened. The wings are long widely spread, approaching a 120° opening angle (photo: © Robert Sadowski www.drzewapolski.pl).

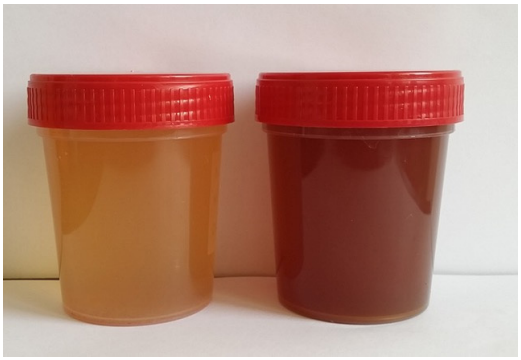

Fig. 7. Urine sample collected from a healthy horse (left) and a horse with EAM (right), showing typical dark red brown colour.

Pathophysiology

Since 2012 the hypoglicyn A is considered to be a factor causing equine atypical myopathy. A metabolite of the hypoglicyn A – methylene-cyclopropylacetic acid (MCPA) reduces the activity of short and medium-chain acetyl-CoA dehydrogenase, resulting in multiple acyl-CoA dehydrogenase deficiency. As a result, beta-oxidation process is interfered. Also the accumulation of fatty acids in the cytosol occurs, which is a characteristic histopathological in EAM, but it is not a pathognomic symptom [Votion *et al.* 2014].

Clinical symptoms

EAM is characterized by subacute or acute general symptoms, which appear within the first 12-24 hours after poisoning [Votion *et al.* 2007b]. At the beginning apathy, lethargy, colic, muscle stiffness and tremors are observed. Significant sweating and muscle weakness also appear. Within hours, EAM-affected horses are unable to stand for longer than a few minutes. Seldom horses remain standing with a ventroflexed head due to muscle weakness. Appetite is usually unchanged or even increased. In the terminal phase total loss of appetite is observed [Palencia *et al*.2007, Votion *et al.* 2007b]. Animals often develop respiratory difficulties and recumbency and the majority die within 72 hours after the onset of signs.

During the clinical examination, congested mucous membranes and hypothermia (below 36,5°C) are noticed [Brandt *et al.* 1997, Palencia *et al.* 2007], although there are some reports of normal or even hyperthermic horses with EAM [van Galen *et al.* 2012]. Initially the heart rate does not change, but with the development of muscle damage it becomes irregular and accelerated because of a cardiomyocyte injury. Heart murmurs and increased respiratory rate are observed. On deep palpation, muscles do not feel particularly firm, painful reactions are rare elicited. Over time, mucous membranes become dark red.

Due to the presence of myoglobin, as a consequence of severe rhabdomyolysis, the urine has a dark brown colour. Absence of myoglobinuria does not exclude EAM. It all depends on the moment of examination of the patient according the onset of clinical signs and the severity of rhabdomyolysis. Myoglobinuria should also be distinguished from haemoglobinuria (the presence of haemoglobin in urine) and from haematuria (the presence of blood in the urine). When rectal palpation is performed, the bladder may feel significantly distended which can contribute to the signs of colic.

Less common clinical symptoms include icterus, haemorrhagic diathesis, head oedema, absence of consciousness, mild diarrhoea, dislocation of colon, penile prolapse, perirenal pain, ptosis and trismus [Brandt *et al*. 1997, Finno *et al.* 2006, Votion *et al.* 2007a, Whitwell *et al.* 1988].

Laboratory examination

In the haematological examination, elevated packed cell volume (PCV) is observed. In horses that died PCV value was significantly higher than in healing ones [Votion *et al*.2007b, van Galen *et al.* 2012]. Also elevated total white blood cell count (WBC) usually due to neutrophilia may occur.

In biochemical analysis, a significant increase of creatinine kinase (CK) activity is observed, rising rapidly in association with the onset of clinical signs to >10,000 IU/L and often reaching >100,000 IU/L [Votion *et al.* 2007b]. However, the increase of CK activity cannot be a prognostic factor because it may only be slightly increased when measured shortly after the onset of clinical signs. Aspartate aminotransferase (AST) serum activity should be also taken into consideration. Serial analysis of the activity of both these enzymes, first every 48-72 hours, then every 7-10 days, is more likely to be effective diagnostic and prognostic tool than measurement only at admission. The most helpful laboratory test to screen for EAM is probably the determination of the serum activities of muscle enzymes and the presence of myoglobin in urine samples. In the initial stage of the disease an increase of lactate concentration (mean value 6,7; ref. < 2 mmol/L) in blood is observed due to lactic acidosis [van Galen *et al.* 2013]. Hyponatremia, hypokalaemia and hypochloraemia appear only in the terminal stage [Votion *et al.* 2007b]. Hyperkalaemia and hypernatremia are less common [van Galen *et al.* 2012]. Moreover, it is recommended to measure the concentration of blood urea and creatinine values which are important markers of a renal function. During the rhabdomyolysis, myoglobin is released into the peripheral blood and accumulates in the kidneys [Plotnikov *et al.* 2009], which can lead to acute renal failure as a result of oxidative stress.

Hyperglycaemia is observed in horses with EAM whereas humans with MADD have hypoglycaemia [Katibi *et al.* 2015]. It is believed that hyperglycaemia in horses reflects a higher ability to mobilize glucose from glycogen in the liver [Votion *et al.* 2007b, Cassart *et al.* 2007]. Studies confirm that horses with EAM show increased serum and urine acylcarnitine and glycine conjugates levels [Bochnia *et al.* 2015, Żuraw *et al.* 2016], although commercial determination of these parameters is not applicable in horses. An ideal parameter helpful in making the final diagnosis of the disease would be to evaluate the increase of hypoglicyn A in the urine and in the blood [Bochnia *et al.* 2015]. Unfortunately, such test is available in few laboratories in the USA.

Postmortem and histopathological findings

The mortality rate due to EAM can be up to 85% [Puyalto-Moussu *et al.* 2004, Votion *et al.* 2004]. The survival rate depends primarily on fast diagnosis of the disease and immediate implementation of treatment. In the post-mortem examination, the urinary bladder is filled with dark brown urine [Cassart *et al*. 2007]. In the stomach content fragments of maple seeds can be observed [Żuraw *et al*. 2016]. Macroscopically, necrotic foci as pale regions in the postural and respiratory muscles are visible. On the

other hand, there are some reports of no macroscopic changes observed in either the skeletal or cardiac muscle [Puyalto-Moussu *et a*l. 2004, Votion *et al.* 2004].

In the histopathological examination myodegeneration, which is morphologically consistent with Zencer's degeneration, is observed. Myofibers show fragmentation, swelling, have a loss of cross striations, and hyaline appears [Palencia *et al.* 2007, Cassart *et al*. 2007]. It is recommended to perform additional tests to reveal the accumulation of fatty acids in cells.

Treatment

Horses with EAM require supportive and nursing care. It is necessary to remove the animal from the pasture as soon as possible and place it in a stable with a deep bedding to prevent the hypothermia and further damage to the body.

There is no specific treatment of EAM. In order to restore circulating volume, correct acid-base and electrolyte imbalances fluid therapy is recommended and it is the first and the most important stage of the therapy. Glucose administration at the dose of 1-4 mg/kg I.V. increases the animal's chances of recovery. Some authors believe that the oral administration is the most beneficial way of carbohydrate supplementation [Votion *et al.* 2007b]. During EAM, there are no such severe pain symptoms as in case of post-exertional myopathies. Depending on the patient's condition it is recommended to implement anti- inflammatory drugs, if necessary, analgesics. Non-steroidal anti-inflammatory drugs (NSAID's) are the most commonly used, but it have to be used with caution because of high probability of co-existing renal damage. Muscle spasm are rare. On the other hand, muscle stiffness and fasciculations have been observed. Administration of muscle relaxants can bring a relief to the animal. However, it should be remembered that medications may increase the already existing muscle weakness.

Supportive treatment includes the administration of antioxidants, such as vitamin E at a dose of 5.000 IU/500 kg b.w.. Horses that received antioxidants (vitamin C, E and selenium) showed higher survival than those in the group without any supplementation [van Galen *et al*. 2012]. However, according to other studies, it did not bring any results [Brandt *et al.* 2007, Hosie *et al.* 1987]

Conclusions

Despite many studies and scientific publications concerning equine atypical myopathy, it is not fully understood. The mechanism of the disease development is not completely clear, which makes it difficult to establish effective treatment guidelines. The therapy is based mainly on symptomatic treatment, consisting of a fluid therapy, anti-inflammatory drugs, analgesic treatment and antioxidant administration. The mortality rate is very high.

In Poland, no cases of disease have been reported so far, although this does not exclude EAM's occurrence.

REFERENCES

1. BAISE E., HABYARIMANA J.A., AMORY H., BOEMER F., DOUNY C., GUSTIN P., MARCILLAUD-PITEL C., PATARIN F., WEBER M., VOTION D.M., 2016 – Samaras and seedlings of Acer pseudoplatanus are potential sources of hypoglicyn A intoxication in atypical myopathy without necessarily inducing clinical signs. ***Equine Veterinary Journal*** 48, 414-417.
2. BOCHNIA M., ZIEGLER J., SANDER J., UHLIG A., SCHAEFER S., VOLLSTEDT S., ZEYNER A., 2015 – Hypoglicyn A Content in Blood and Urine Discriminates Horses with Atypical Myopathy from Clinically Normal Horses Grazing on the Same Pasture. ***PLoS ONE*** 10, 9-11.
3. BOWEN, J.N., CRAIG, J.F., 1942 - Myoglobinuria in horses. ***The Veterinary Records*** 35, 354.
4. BRANDT K., HINRICHS U., GLITZ F., LANDES E., SCHULZE C., DEEGEN E., POHLENZ J., COENEN M., 1997 – Atypische myoglobinurie der weidepferde. ***Pferdeheilkunde*** 13, 27-34.
5. CASSART D., BAISE E., CHEREL Y., 2007 – Morphological alterations in oxidative muscles and mitochondrial structure associated with equine atypical myopathy. ***Equine Veterinary Journal*** 39, 26-32.
6. FINNO C.J., VALBERG S. J., WUNSCHMANN A., MURPHY J.M., 2006 – Seasonal pasture myopathy in horses in the midwestern United States: 14 cases (1998-2005). ***Journal of American Veterinary Medical Association*** 229, 1134-1141.
7. GERBER V., STRAUB R., FREY J., 2006 – Equine botulism and acute pasture myodystrophy: new soil-borne emerging diseases in Switzerland? ***Schweizer Archiv Fur Tierheilkunde*** 148, 553-559.
8. HOSIE B.D., GOULD P.W., HUNTER A.R., LOW J.C., MUNRO R., WILSON H.C., 1987 – Acute myopathy in horses at grass in east and south east Scotland. ***Veterinary Records*** 119, 444-449.
9. KARLÍKOVÁ R., ŠIROKÁ J., JAHN P., FRIEDECKÝ D., GARDLO A., JANEČKOVÁ H., HRDINOVÁ F., DRÁBKOVÁ Z., ADAM T., 2016 – Equine atypical myopathy: A metabolic study. ***The Veterinary Journal*** 216, 125-132.
10. KATIBI O.S., OLAOSEBIKAN R., ABDULKADIR M.B., OGUNKUNLE T.O., IBRAHEEM R.M., MURTALA R., 2015 – Ackee Fruit Poisoning in Eight Siblings: Implications for Public Health Awareness. ***The American Journal of Tropical Medicine and Hygiene*** 93,1122-1123.
11. MCKENZIE R.K., HILL F.I., HABYARIMANA J.A., BOEMER F., VOTION D.M., 2016 – Detection of hypoglicyn A in the seeds of sycamore (Acer pseudoplatanus) and box elder (A. negundo) in New Zealand; the toxin associated with cases of equine atypical myopathy. ***New Zealand Veterinary Journal*** 64, 182-187.
12. PALENCIA P., RIVERO J.L.L., 2007 – Atypical myopathy in two grazing horses in northern Spain. ***Veterinary Records*** 161, 346-348.
13. PLOTNIKOV E.Y., CHUPYRKINA A.A., PEVZNER I.B., ISAEV N.K., ZOROV D.B., 2009 – Myoglobin causes oxidative stress, increase of NO production and dysfunction of kidney's mitochondria. ***Biochimica et Biophysica Acta*** 1792, 796-803.
14. PUYALTO-MOUSSU C., SAISON A., LECONTE D., 2004 – Myoglobinurie atypique: e pidemiologie de cas Franc caise de myopathie aigue. ***Pratique Vétérinaire Équine*** 36, 29-35.
15. UNGER L., NICHOLSON A., JEWITT E. M., GERBER V., HEGEMAN A., SWEETMAN L., VALBERG S., 2014 – A Concentrations in Seeds of Acer Pseudoplatanus Trees Growing on Atypical Myopathy-Affected and Control Pastures. ***Journal of Veterinary Internal Medicine*** 28, 1289-1293.
16. VALBERG S.J., SPONSELLER B.T., HEGEMAN AD., EARING J., BENDER J.B., MARTINSON K.L., PATTERSON S.E., SWEETMAN L., 2013 – Seasonal pasture myopathy/atypical myopathy in North America associated with ingestion of hypoglicyn A within seeds of the box elder tree. ***Equine Veterinary Journal*** 45, 419-426.
17. VAN GALEN C., MARCILLAUD PITEL C., SAEGERMAN C., 2012 – European outbreaks of atypical myopathy in grazing equids (2006-2009): spatiotemporal distribution, history and clinical features. ***Equine Veterinary Journal*** 44, 614-620.

18. VAN GALEN G., CERRI S., PORTER S., SAEGERMAN C., LEFERE L., ROSCHER K., MARR C., AMORY H., VOTION DM., 2013 – Traditional and quantitative assessment of acid-base and shock variables in horses with atypical myopathy. ***Journal of Veterinary Internal Medicine*** 27,186-193.
19. VOTION D. M., HAHN C. N., MILNE E.M., 2007a – Concurrent conditions in single cases: the need to differentiate equine dysautonomia (grass sickness) and atypical myopathy, ***Equine Veterinary Journal*** 39, 390-392.
20. VOTION D. M., VAN GALEN G., SWEETMAN L., BOEMER F., DE TULLIO P., DOPAGNE C., LEFÈRE L., 2014 – Identification of methylenecyclopropyl acetic acid in serum of European horses with atypical myopathy. ***Equine Veterinary Journal*** 46, 146-149.
21. VOTION D.M., AMORY H., DEMOULIN V., DESMECHT D., ROLLIN F., THIRY E., BAISE E., CASSART D., DELGUSTE C., PIAT E., SANDERSEN C., LINDEN A., 2005 – Atypical myopathy (atypical myoglobinuria). In: IVIS (Ed.), IVIS ***Reviews in Veterinary Medicine International Veterinary Information Service,*** Ithaca. R0101.1104.
22. VOTION D.M., LINDEN A., DELGUSTE C., AMORY H., THIRY E., ENGELS P., VAN GALEN G., NAVET R., SLUSE F., SERTEYN D., SAEGERMAN, C., 2009 – Atypical myopathy in grazing horses: A first exploratory data analysis. ***The Veterinary Journal*** 180, 77-87.
23. VOTION D.M., LINDEN A., SAEGERMAN C., ENGELS P., ERPICUM M., THIRY E., DELGUSTE C., ROUXHET S., DEMOULIN V., NAVET R., SLUSE F., SERTEYN D., VAN GALEN G., AMORY H., 2007b – History and clinical features of atypical myopathy in horses in Belgium (2000–2005). ***Journal of Veterinary Internal Medicine*** 21, 1380-1391.
24. WATMOUGH, N.J., FRERMAN, F.E., 2010 – The electron transfer flavoprotein: Ubiquinone oxidoreductases. ***Biochimica et Biophysica Acta*** 1797, 1910-1916.
25. WHITWELL, K.E., HARRIS, P. AND FARRINGTON, P.G., 1988 – Atypical myoglobinuria: an acute myopathy in grazing horses. ***Equine Veterinary Journal*** 20, 357-363.
26. ŻURAW A., DIETERT K., KÜHNEL S., SANDER J., KLOPFLEISCH R., 2016 – Equine atypical myopathy caused by hypoglicyn A intoxication associated with ingestion of sycamore maple tree seeds. . ***Equine Veterinary Journal*** 48, 418-421.