Surveillance Focus

An ongoing concern: 20 years of research on equine atypical myopathy

Anne-Christine François, **Benoît Renaud**, **Caroline-Julia Kruse**, **Christel Marcillaud-Pitel** and **Dominique-Marie Votion** of the Atypical Myopathy Alert Group discuss insights from 20 years of research and surveillance on equine atypical myopathy.

EQUINE atypical myopathy (AM) is a severe form of plant poisoning that affects equids at pasture and is associated with a high mortality rate.[1] AM occurs following the ingestion of protoxins present in seedlings[2] and fruits[3,4] of *Acer* species trees, primarily *Acer pseudoplatanus* in temperate European regions[5] (Fig 1) and *Acer negundo* in North America.[6]

In Europe, AM outbreaks are observed mainly in spring (March to May) and autumn (October to December), predominantly affecting horses that spend more than six hours per day at pasture.[7]

Clinical signs of AM include depression, weakness, stiffness, lateral recumbency, trembling and sweating[1,8] and reflect the severe rhabdomyolysis syndrome that affects postural, respiratory and cardiac muscles, accompanied by pigmenturia.[9]

The incriminated protoxins are methylenecyclopropylalanine, known as hypoglycin A (HGA), and methylenecyclopropylglycine (MCPrG), which themselves are not toxic.[5,6,10] However, a two-step metabolic process gives rise to two toxic compounds (methylenecyclopropylacetyl-CoA [MCPA-CoA] for HGA and methylenecyclopropylformyl-CoA [MCPF-CoA] for MCPrG)[11] which disrupt the β-oxidation of fatty acids, predominantly in skeletal muscles.[12]

A presumptive diagnosis of AM is multifactorial and relies on combining elements of:

- recent history such as time spent at pasture and season;
- the environment, such as the presence of toxic trees around the pasture;
- physical examination confirming typical clinical signs; and
- evidence of an acute myopathic syndrome suggested by pigmenturia and/or confirmed by severe elevated serum creatine kinase levels.[1,7,8,13–15]

In 2004, the Atypical Myopathy Alert Group (AMAG) was established to alert practitioners and horse owners in Belgium when AM outbreaks were reported. The network expanded to Europe in 2006 with close collaboration with the Réseau d'Épidémio-Surveillance en Pathologie Équine (RESPE) network, which tracks French cases.

> **Equine atypical myopathy is a severe form of plant poisoning that affects equids at pasture**

The cause of AM was discovered just over 10 years ago,[5,6] and since then several laboratories have provided analyses of protoxins and toxic metabolites. The presence of protoxins in blood confirms exposure to poisonous trees, while the presence of toxic metabolites (MCPA and/or MCPF conjugates), in association with a severely altered acylcarnitines profile, provides a definitive diagnosis.[16] Although acylcarnitine profiling is increasingly available in diagnostic laboratories, it is not routinely performed. As a result, AM diagnosis is typically based on presumptive findings.[6]

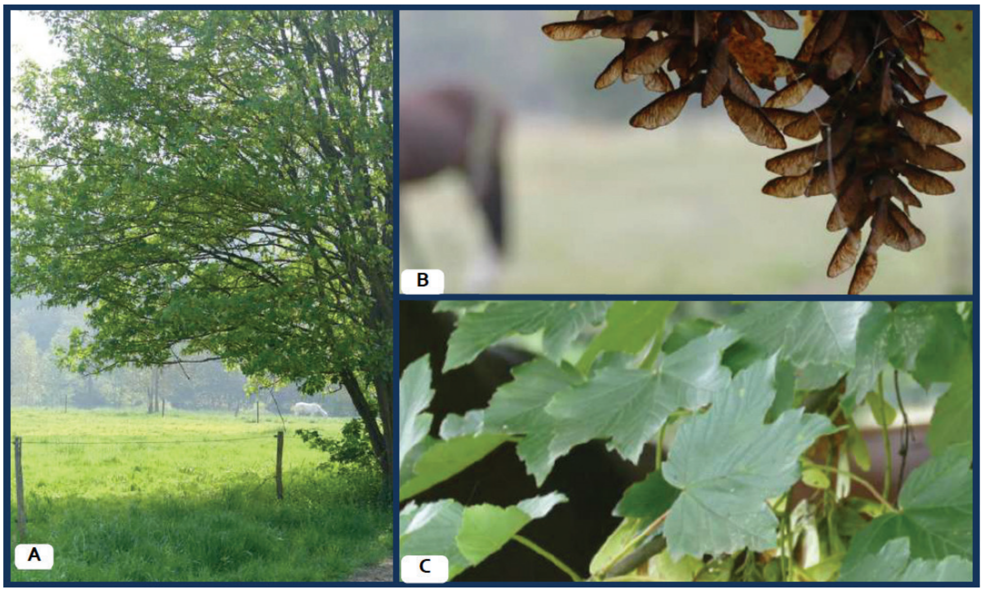

Fig 1: *Acer pseudoplatanus* (A) appearance on pasture, (B) fruits and (C) leaves

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This article provides an overview of presumptive cases reported to AMAG over the past 18 years, with a focus on the situation in the UK.

Collecting data from European AM cases

Information about European AM cases over an 18-year period (2006–2023) was collected via standardised questionnaires available on the AMAG (http://www.myopathie-atypique.be) and RESPE (https://respe.net) websites. These were completed via email or telephone contact with owners (for management and environment information) and/or veterinarians (for clinical data) whenever feasible.

Cases were classified as 'autumnal' cases when occurring in the six months between the beginning of September and the end of February, whereas 'spring' cases occurred between the beginning of March and the end of August.[7]

Between 2006 and December 2023, 3199 European AM cases were recorded by AMAG in association with RESPE. The five countries reporting the highest total number of cases were France (1310), Belgium (782), the UK (412), Germany (314) and the Netherlands (111), with Hungary reporting its first case to AMAG in autumn 2022 (Fig 2).

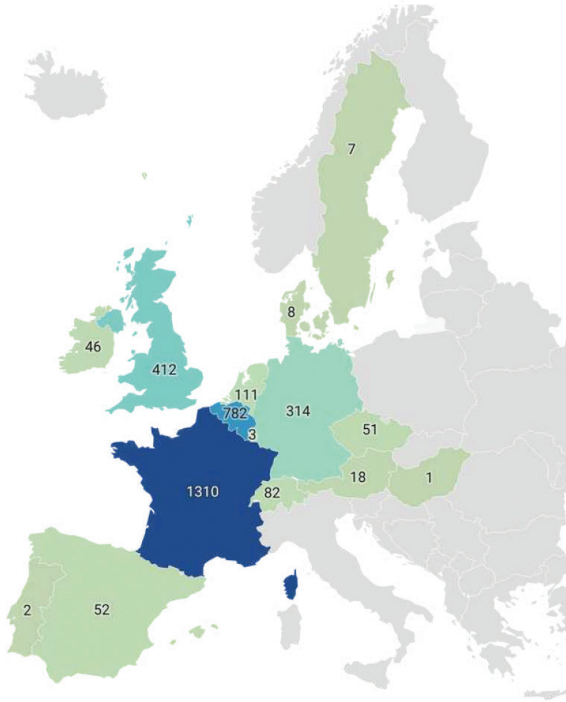

Fig 2: European distribution of atypical myopathy cases notified to disease surveillance networks between autumn 2006 and December 2023

The number of cases reported annually fluctuates greatly, probably due to multiple factors that vary each year. These include the invasive character of *Acer* species trees and the quantity of fruits they produce, which can vary year-on-year along with protoxin production levels. Weather conditions may affect the production and dispersal of toxic fruits, as well as pasture quality, both of which are key factors influencing exposure, particularly during years of intense fruiting. The abundance of these fruits and horses' access to contaminated pastures are key factors, with the latter being subject to modulation by climatic conditions.

Increased awareness and reporting practices also contribute to fluctuations in case numbers not only across years but also between countries. Indeed, the voluntary nature of reporting may influence the feedback obtained by AMAG. In some countries, like France, a network of sentinel veterinarians routinely reports several diseases, including pasture-associated conditions, potentially making their case reporting more consistent. The fact that the online questionnaires for reporting suspected AM cases are not translated into all European languages may also present a barrier to spontaneous and regular reporting.[8]

AM in the UK

Historically, the first reports of European AM outbreaks in the veterinary literature occurred during the 1980s from England and Scotland.[17,18] The shift from anecdotal to recurrent reports of the condition underlines the emerging nature of AM and reflects a possible increase in awareness in recent years.

However, since the last published inventory in 2019,[7] only five cases have been added to the UK AM case count (four in autumn 2022 and one in spring 2023), despite a corresponding rise in case numbers across other European countries (Fig 3). This may suggest that since the end of 2019 cases of AM have been underreported from the UK.

A total of 412 presumed cases of AM have been reported to AMAG from the UK since 2006. In these reports, 261 locations were given, either as the address of the owner or of the pasture, and 197 reports indicated the specific location of the pasture where the suspected AM case was grazing and represented a total of 155 different UK towns, mainly in the southern half of England (Fig 4).

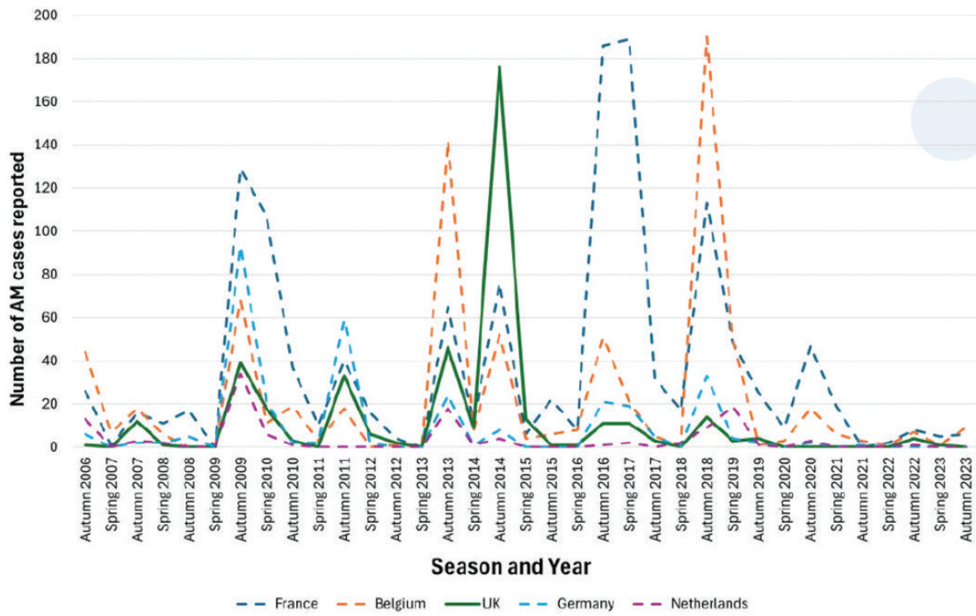

Fig 3: Time course (season and year) of atypical myopathy cases reported to the Atypical Myopathy Alert Group since autumn 2006 by each of the top five reporting countries (France, Belgium, UK, Germany and the Netherlands)

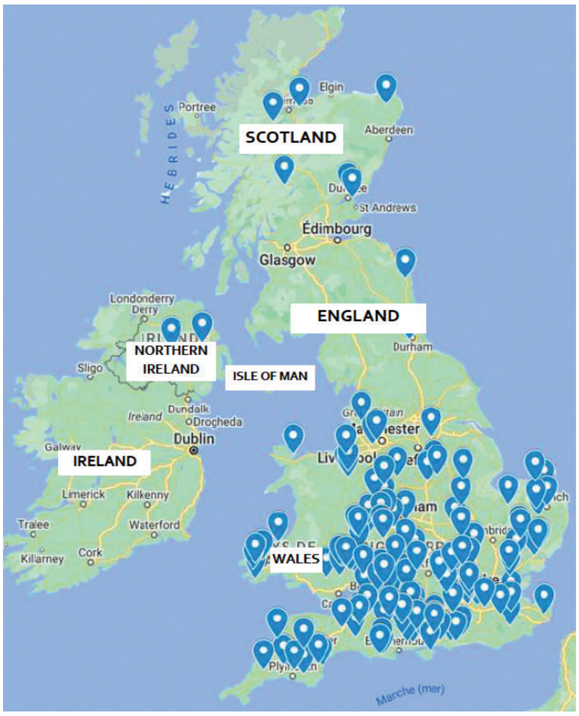

Fig 4: Distribution of 197 atypical myopathy cases across the UK between 2006 and 2023, mapped at the town level (n=155)

Value of surveillance

Epidemiological surveillance over the years has led to the collection of substantial information about AM cases in Europe.[4,8,19–24] Thanks to these data, epidemiological analyses of European cases have enabled characteristics of the disease to be highlighted, such as high-risk seasons,[8] mortality rate,[13] most frequent clinical signs[1] and environmental features, such as the link with weather conditions and with the presence of *A pseudoplatanus* in pastures.[8] Preventive measures, such as avoiding permanent grazing,[15] as well as risk and prognostic factors[14] have also been identified.

A clinically relevant diagnostic algorithm, used to categorise cases reported to AMAG, and the ability for practitioners to refer to this algorithm[1] have helped in the recognition of AM. This and other information has ultimately contributed to the discovery of the cause of AM while analysing AM cases registered by AMAG between 2006 and 2019 enabled researchers to address the most frequently asked questions regarding horse feeding and management practices to reduce the risk of AM.[7]

> **Since the end of 2019 cases of atypical myopathy may have been under-reported from the UK**

However, the story is not over, and the threat of AM persists and may even be increasing due to climate change and the invasive nature of *A pseudoplatanus*. The reduction of case reporting in the UK since 2019 prevents the identification of any potential specificities and hinders the ability to maintain vigilance during high-risk periods, which relies on up-to-date surveillance.

The latest information from case reports and targeted field studies has revealed that this plant poisoning can affect other herbivore species,[25–27] where the existence of subclinical cases has been suggested.[27] To this end *A pseudoplatanus* poisoning has also been demonstrated in Père David's deer,[25] camels[26] and gnus[27] and, concerningly, the protoxins can pass into cow's milk, a foodstuff of animal origin that may be consumed by people.[28–30] Transfer of these toxins to milk has also been confirmed in mares with or without clinical disease, thereby posing a risk to foals during suckling.[31,32]

Recent publications by Renaud and colleagues refine the diagnostic and prognostic criteria for AM, but more worryingly, clearly demonstrate the existence of subclinical cases among co-grazers with equids.[16,27]

Concluding remarks

The collection of data from AM cases remains essential to advancing research into the exact mechanisms of this intoxication and the quest to discover of a treatment that directly counteracts the action of the toxic molecules. Until now, treatment has been symptomatic rather than targeted and aetiological, and the mortality rate remains high in horses at 74 per cent[1] and slightly lower at 56 per cent among hospitalised horses.[24]

Using various samples collected by AMAG, new, alternative and ethically acceptable research methods are being developed, avoiding wherever possible the need to use animals in research.[33]

With this brief article, we hope to raise awareness among horse owners and veterinary surgeons about the continued seasonal danger from the toxic plant insult of AM. We encourage both owners and vets to report AM cases to the AMAG network to help to establish a responsive alert system. Retrospective reporting of cases occurring before autumn 2024 is also possible (and encouraged) and offers the benefit of gaining a better understanding of the European situation over time.

REPORTING CASES OF EQUINE ATYPICAL MYOPATHY

To report a case of atypical myopathy go to http://atypicalmyopathy.uliege.be/ and choose between owner and veterinary reporting

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