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CLINICAL COMMENTARY

Atypical myopathy associated with box elder in Europe

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The case report by Jahn et al. (2025) describes a case of atypical myopathy in Europe caused by ingestion of the protoxin hypoglycin A (HGA) from box elder seedlings. This is an important report. It reminds clinicians in Europe that trees other than The European sycamore (*Acer pseudoplatanus*) may contain HGA and that there is a potential for other unfamiliar plant species to cause pasture-associated toxicities.

After many years of research, the pathogenesis of atypical myopathy, also known as seasonal pasture myopathy, is now well understood. The severe myopathy results from the ingestion of the seeds or seedlings of European sycamore (*Acer pseudoplatanus*) in Europe and the box elder (*Acer negundo*) in the USA (Valberg et al., 2013; Westermann et al., 2008). The seeds, seedlings, and leaves of these trees contain the protoxin HGA, and to a lesser extent its analogue methylenecyclopropylglycine (MCPrG; Bochnia et al., 2019). These protoxins are metabolised to the active toxins methylenecyclopropylacetyl-CoA (MCPA-CoA) and MCPrG-CoA, respectively, at tissue-specific rates and primarily in skeletal muscle (Sander et al., 2023). The toxic effects mainly occur in the highly-oxidative 'slow-twitch' type I muscle fibres such as the postural muscles, masseters, diaphragm and cardiac muscle (Cassart et al., 2007). The primary toxin, MCPA-CoA inhibits acyl-CoA dehydrogenase enzymes involved in the beta-oxidation of fatty acids and catabolism of branched-chain amino acids resulting in failure of mitochondrial energy generation and subsequently muscle cell death (Westermann et al., 2008). Inhibition of Acyl-CoA dehydrogenase enzymes causes an accumulation of their acyl-CoA substrates and the carnitine and glycine conjugates of those substrates in serum and urine, a characteristic metabolic profile known as multiple acyl-CoA dehydrogenase deficiency (MADD) (Westermann et al., 2008). The accumulation of acylcarnitines together with the protoxins (HGA and MCPrG) and the carnitine conjugates of the toxins (MCPA-carnitine and MCPF-carnitine) can be detected in serum by liquid-chromatography-mass-spectometry (LCMS) (Bochnia et al., 2019; González-Medina et al., 2021; Valberg et al., 2013).

In many cases a diagnosis of atypical myopathy can be made relatively confidently based on the characteristic clinical signs, serum biochemical changes, the seasonal occurrence and, in Europe, the presence of sycamore (*Acer psuedoplatanus*) seeds or seedlings on the pasture (Dunkel et al., 2018; González-Medina et al., 2017). Detection of serum HGA or MCPA-carnitine by LCMS may be useful to confirm the diagnosis and may be particularly useful to identify sub-clinically affected cases, or those with less-severe or unusual presentations or when a toxic (tree) source cannot readily be identified.

HGA or MCPA-carnitine has been detected in the serum of horses co-grazing with affected cases (Baise et al., 2016; Bochnia et al., 2018; Renaud et al., 2024). Whilst these co-grazing horses were apparently healthy it is unknown whether clinical signs would have been apparent if they had undertaken higher levels of exercise or if they could have been precipitated by a greater negative energy balance, requiring a greater reliance on metabolism of stored fats. It is therefore plausible that HGA could affect the exercise performance of a much greater number of horses than those with overt clinical signs.

Identification of serum HGA or MCPA-carnitine can also be useful in cases such as the case described by Jahn et al. (2025) in which box elder but not sycamore trees were present on the pasture. Whilst the presence of box elder had been reported on one European pasture grazed by an AM-affected horse previously, sycamore was also present on that pasture (Votion et al., 2014) and to the author's knowledge, confirmed box elder related atypical myopathy has not been reported previously in Europe.

Many clinicians in Europe will not be familiar with the box elder tree as an alternative source of HGA, However, given that the box elder has been identified as a major invasive species in forests in

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the European Union (Campagnaro et al., 2018), it is likely to be responsible for further cases of atypical myopathy in Europe in future. Clinicians should also be aware of the potential for many other trees of the *Acer* family that are grown in gardens or as ornamental trees to contain HGA. HGA has been identified in the sugar maple (*Acer saccharum*), Japanese maple (*Acer palmatum*), trident maple (*Acer buergerianum*), paperbark maple (*Acer griseum*), Himalayan maple (*Acer oblongum*), mountain maple (*Acer spicatum*), big leaf maple (*Acer macrophyllum*), full moon maple (*Acer* japonicum), lime-leafed maple (*Acer distylum*) and Siebold's maple (*Acer sieboldianum*; Fowden & Pratt, 1973; Novotná et al., 2023). Given the potential for the winged samaras of these species to spread widely in windy conditions, it is plausible that cases of atypical myopathy could occur if these species are grown in gardens adjoining paddocks.

Acylcarnitine profiling combined with HGA/MCPA-carnitine assays may also be clinically useful to identify unusual cases of atypical myopathy, other pasture toxicities and inborn errors of metabolism. For example, a rare case of atypical myopathy was diagnosed using these methods in a newborn foal in which the mare had suffered from atypical myopathy during pregnancy (Karlíková et al., 2018). In another case, severe clinical signs in a newborn foal resulted from suspected concurrent atypical myopathy with inborn metabolic disease (Sander et al., 2021). Finally, acylcarnitine profiling was also successfully used to identify an inborn form of MADD without HGA toxicity in a Paint foal (Pinn et al., 2018).

Recently, acylcarnitine profiling was also used to identify cases of marsh mallow (*Malva parviflora*) toxicity in which it is proposed that malvalic and/or sterculic acid inhibit very-long-chain acyl-CoA dehydrogenase, thus slowing the beta-oxidation of very-long-chain fatty acids (Bauquier et al., 2017). Acylcarnitine profiles have also revealed suspected disorders of fatty acid metabolism without the detection of HGA MCPA-carnitine in serum samples submitted to the authors' laboratory (unpublished data) and it is likely that as yet unidentified pasture-associated toxicities occur in the UK and Europe.

In conclusion, the interesting case report by Jahn et al. (2025) is an important reminder to clinicians in Europe of the potential for *Acer* species other than sycamore to cause atypical myopathy. Acylcarnitine profiles and detection of HGA/ MCPA-carnitine by LCMS can be a useful diagnostic aid in myopathy cases.

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E. J. Knowles: Writing – original draft. **R. J. Piercy:** Writing – review and editing.

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ETHICS STATEMENT

Not applicable to this clinical commentary.

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