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CASE REPORT

OTHER

Subclinical thiamine deficiency results in failed reproduction in Arctic foxes

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Abstract

Thiamine deficiency can result in life-threatening physiological and neurological complications. While a thiamine-deficient diet may result in the onset of such symptoms, the presence of thiaminase – an enzyme that breaks down thiamine – is very often the cause. In such instances, thiaminase counteracts the bioavailability and uptake of thiamine, even when food-thiamine levels are adequate. Here, we report on a case of failed reproduction in seven Arctic fox (*Vulpes lagopus*) breeding pairs kept at a captive breeding facility, including the presentation of severe thiamine deficiency symptoms in two male foxes. Symptoms included ataxia, obtundation, truncal sway, star-gazing and visual impairment. Blood tests were inconclusive, yet symptoms resolved following treatment with a series of thiamine hydrochloride injections, thereby verifying the diagnosis. A fish-dominated feed, which for the first time had been frozen for a prolonged period, was identified as the likely source of thiaminase and subsequent deterioration in the animals' health. Symptoms in the two males arose during the annual mating period. All seven breeding pairs at the captive breeding station failed to reproduce – a phenomenon never recorded during the captive breeding facility's preceding 17-year operation. Relating our findings to peer-reviewed literature, the second part of this case report assesses how thiamine deficiency (due to thiaminase activity) likely resulted in subclinical effects that impaired the production of reproduction hormones, and thereby led to a complete breeding failure. While previous work has highlighted the potentially lethal effects of thiamine deficiency in farmed foxes, this is, to our knowledge the first study showing how subclinical effects in both males and females may inhibit reproduction in foxes in general, but specifically Arctic foxes. The findings from our case report are not only relevant for captive breeding facilities, but for the welfare and management of captive carnivorous animals in general.

KEYWORDS
breeding, physiology-reproductive, pregnancy, wildlife

1 | INTRODUCTION

Thiamine (vitamin B1) is essential to all living organisms and its biological importance has been known for over 100 years (Kraft & Angert 2017). It is necessary for carbohydrate metabolism and plays an important role in numerous cellular metabolic processes, hormone production and neural functions (Hammer & Hafez 2018; Manzetti et al. 2014; Pacei et al. 2020; Ramakrishna 1999). Most animals, including humans, are unable to synthesise thiamine and all thiamine is obtained from dietary sources (Markovich et al. 2013). Since thiamine is water soluble, heat sensitive, unstable in alkaline environments, has a short half-life (1–12 h) and can only be stored in the body for 1–3 weeks (Pacei et al. 2020), a regular dietary supply is required to maintain sufficient levels.

Thiamine supplementation in commercially available animal feeds consists primarily of synthetic sources (thiamine mononitrate and thiamine hydrochloride) which degrade more readily than thiamine found in plant and animal products (Marks et al. 2011). Providing stable, reliable concentrations of thiamine in animal feed can be challenging, as evidenced by numerous recalls of animal food due to a lack of thiamine (Kritikos et al. 2017). These situations arise despite the feed having been produced by reputable companies with a strong emphasis on nutritional quality (Markovich et al. 2014). The use of raw fish in animal feed may further compromise the stability of thiamine levels (Croft et al. 2013). Many fish species are rich in the enzyme thiaminase, which breaks down thiamine (Geraci 1972). Thiaminase is thought to also degrade thiamine in the gut of animals that consume fish (Fitzsimons et al. 2012). Thiamine is absorbed into the blood via the gastrointestinal tract and the consumed thiaminase activity persists in the animals' digestive tracts, inhibiting the uptake of thiamine. Providing a balanced diet for non-domesticated species held in captivity may therefore potentially be more challenging, as commercially available balanced feeds, as well as reference values for various vital nutrients, are often lacking. This has proved problematic for a variety of animal taxa held in captivity, including fish (Harder et al. 2020), reptiles (Rowland 2016), marine mammals (Gimmel et al. 2016), amphibians (Wright & Whitaker 2001), birds (Carnarius et al. 2005; Peter et al. 2002) and even large terrestrial carnivores (Cynthia et al. 2005). Thiamine deficiency in animals can result in several clinical symptoms, including vomiting, inappetence, diarrhoea, ataxia, seizures, obtundation, truncal sway and visual impairment or blindness (Carnarius et al. 2005; Houston & Hulland 1988; Kritikos et al. 2017; Marks et al. 2011; Moon et al. 2013; Okada et al. 1987; Vernau et al. 2015). Once advanced, symptoms are very apparent due to the neurological effects. The importance of subclinical levels of thiamine deficiency, that is when reduced thiamine levels do not result in any obvious symptoms, yet affect the physiological functioning of the body, are recognised (Alrubaye Hisham et al. 2021; Heller et al. 1974; Thomas 1986). However, standard haematological and blood biochemistry analyses are typically unremarkable even when deficiencies have resulted in severe symptoms (Marks et al. 2011), thereby making the detection of subclinical deficiencies even more difficult. In addition, there remains a dearth of information on thiamine reference values for many animal species.

Captive breeding is a widely employed conservation strategy used to save threatened species and/or populations from extinction. In Norway, a captive breeding facility was established to breed endangered Arctic foxes, with the offspring released into the wild to re-establish locally extinct populations or strengthen small populations (Landa et al. 2017). Here, we report on an incidence of food-related thiamine deficiency that resulted in advanced clinical symptoms in two foxes, while subclinical effects are suspected to have resulted in reproductive failure in all seven breeding pairs in 2022.

1.1 | Background: The Arctic fox captive breeding facility

During the early 2000s, there were as few as 50–60 Arctic foxes (*Vulpes lagopus*) remaining in Fennoscandia (Angerbjörn et al. 2013). Several conservation measures were initiated to save the Critically Endangered species from local extinction, including a captive breeding programme in Norway (Landa et al. 2017).

The captive breeding station was constructed in 2005 and consists of nine large enclosures (Figure 1) and is located in the species' natural habitat and historical range. In January–February each year, the captive-bred offspring are independent of their parents and are strategically released in selected tundra areas to either re-establish or increase population numbers. Between 2006 and 2022, a total of 460 captive-born offspring have been released into the wild, playing a major role in the species being down-listed from Critically Endangered to Endangered in November 2021 (Eldegard et al. 2021). For detailed overview of the captive breeding programme, see Landa et al. (2017).

Since the inception of the programme, foxes have been fed with feed produced for the fur fox industry (Landa et al. 2017). This feed is nutritionally balanced and meets the species' dietary needs. Although primary ingredients, such as fish products, were frozen prior to feed production, the final product was kept cool (+1 to +4 C°) and served fresh to foxes. In addition, a standard vitamin mixture developed for foxes was added to the feed. This ensured that the various components in the feed were nutritionally intact when ingested. Feed composition and nutritional values were in accordance with established standards for the fox farming industry (Einarsson & Skrede 1989).

In June 2019, the Norwegian parliament approved a new legislation that would see all forms of the fur industry banned by 1 February 2025. As a result, the majority of fur farms ceased production at the end of 2020. This consequently led to the shutting down of several companies that had formally produced food for the fur industry. To ensure a reliable supply of feed for the captive breeding station, a large batch of feed was produced and frozen during January–February 2021. The general nutritional integrity of the frozen food was guaranteed for at least 2 years, and a total of ten tonnes were produced, as this was expected to meet the station's needs for at least 2 years.

The standard feed was comprised of 45% fish products which was frozen prior to processing and inclusion in the fox food, but not cooked/boiled. This consequently did not deactivate thiaminase, an enzyme common in the viscera of many fish species, with well

FIGURE 1 The large enclosures, approximately 50 m × 50 m in size, at the Arctic fox captive breeding station.

documented negative effects in farmed foxes (Einarsson & Skrede 1989; Okada et al. 1987) and many other species that consume raw fish (Croft et al. 2013; Geraci 1972; Gimmel et al. 2016; Houston & Hulland 1988). Since fish viscera have little commercial value for human consumption, they are readily included in animal feed. Thiaminase concentrations differ widely among fish species, but can also fluctuate considerably within species at different times of the year (Tillitt et al. 2005). This fluctuation in thiaminase concentration in fish received by facilities producing fox food was well recognised (Einarsson & Skrede 1989). To mitigate potentially negative effects, the food producer routinely added 30 mg of thiamine hydrochloride to each kilogram of feed.

The former practice of feeding foxes with freshly produced food ensured that there were adequate concentrations of thiamine. However, long-term freezing of the final product had not previously been undertaken. Research shows that although freezing can preserve thiamine in the food, the presence of thiaminase can denature thiamine, even when frozen (Gimmel et al. 2016).

1.2 | Case report 1: Clinical symptoms in two adult male Arctic foxes

The first instance of thiamine deficiency was noticed on 26 April 2022. A 4-year-old male (ID code AF5741) was observed to be ataxic, displaying head sway, and impaired vision was suspected based on behavioural observations. The fox was not lethargic, displayed otherwise normal behaviour and did feed. This male had previously proved to be extremely trap shy and numerous attempts to trap him were unsuccessful. At this point, the den used by the pair in enclosure 8 was covered by approximately 3 m of snow. His balance improved slightly over the coming weeks, and he seemed in otherwise good shape. Eight weeks later, after much of the snow had melted, it was possible to block the entrance to the artificial den and manually capture him using a neck-hold fox handling tool. He was then placed in a temporary holding facility at the breeding station. Handling of foxes at the station is rare as a hands-off approach is practiced, keeping the animals as wild as possible. Given their unhabituated nature, adult foxes resist capture and handling. In contrast to more typical behavioural responses, the male did not resist capture or handling. He was easily captured in the den and transferred to the holding pen. This subdued behaviour was repeated when handled upon inspection by the veterinarian.

Upon examination by the veterinarian, thiamine deficiency was suspected. The male was therefore treated with injections (0.5 mL) of thiamine hydrochloride (44.59 mg/mL; Corébral®, France) administered every day for 7 days.

Blood samples revealed an initial thiamine level of 200.5 μg/L. A value of 167.8 μg/L was obtained when tested 4 weeks later. Based on the test results, the thiamine value was lower during the second test. Thiamine deficiency is poorly reflected in routine bloodwork and highlights the difficulty in using standard blood tests to reliably diagnose thiamine deficiency (Kritikos et al. 2017; Marks et al. 2011; Moon et al. 2013). Despite the apparent lower levels, symptoms had resolved and the fox had recovered, thus serving as valuable diagnostic confirmation. Only minor coordination/ataxia was evident 4 weeks after treatment, but as reported elsewhere, such symptoms may take several weeks or months to resolve completely (Chang et al. 2017). The male's ataxic behaviour resolved within a few weeks.

Thiamine deficiency can also impact liver function and may be evidenced by increased levels of alanine transferase (ALT) in the blood, a commonly used biomarker for liver function. Compared to reported reference values for farmed Arctic foxes which ranged between approximately 40–80 U/L (Lorek et al. 2002; Rotkiewicz & Janiszewski 2010; Saba et al. 2009), AF5741 had 378 U/L. Similarly, low amylase levels may indicate liver, kidney or pancreas problems, and with a value of 479, it was well below a mean reference value of 674.0 U/L (Benn et al. 1986).

The second instance involved a 1-year-old male (ID code AF5878) that was detected during early June 2022. The same general symptoms as described above were observed in this instance too. This male however displayed excessive star gazing behaviour and more pronounced ataxia. He too was not lethargic and spent prolonged periods running around the enclosure. The star gazing behaviour was particularly evident when he attempted to turn around and run in the opposite direction. His head would be raised skywards as a turn was initiated, but the head would not rotate and orientate synchronously with the rest of with his body. Once captured and placed in the temporary holding pen, his poor balance and excessive swaying gait were evident.

AF5878 received the same series of daily IM injections as described above. Blood thiamine levels were first recorded as 102.8 μg/L and then 132.7, 4 weeks later. ALT was 209 U/L (reference value range 40–80 U/L). Unfortunately, amylase levels were not returned from the laboratory. Four weeks later the fox's amylase level was 325 U/L (mean reference value 674.0 U/L). A complete overview of all blood parameters that were tested are presented in Table S1. General improvement was observed, the severe ataxia and wobbly head resolved, and he was released back into his enclosure. A slightly uncoordinated gait was evident, but otherwise the fox appeared well.

Both males were born in the wild and brought to the captive breeding station as 3-month-old puppies from the same sub-population. Neither of the foxes had displayed such symptoms earlier, or were known to have any other health issues. During the 4 weeks the foxes were held in the temporary holding pens for observation, their weights remained stable (AF5871: 3,3 kg, AF5878: 3,5 kg).

On 21 September 2022, shortly before changing the food permanently, it was noticed that the star gazing behaviour had reappeared in AF5878, although not as severe as in June. The fox was trapped the following day and given daily thiamine injections (0.5 mL) for 7 days. Upon trapping, visual impairment was suspected. He was released back into the enclosure 2 weeks after being trapped when both the star-gazing behaviour and other symptoms had resolved. In cats, for example, it can take several months for advanced neurological symptoms to fully resolve (Chang et al. 2017). The onset of the second round of symptoms coincided with the production of winter fur. Thiamine is required in greater quantities during periods of growth, or when females are pregnant. The greater energetic demands of winter fur production, in combination with a potential predisposition for lower thiamine levels, may therefore have resulted in the onset second round of symptoms. During the second treatment of this fox, the food was changed to a meat diet that did not include any fish. He thereafter recovered fully and did not display symptoms again. This new diet was provided to all the foxes at this time and continues to be used to date.

1.3 | Case report 2: Failed reproduction in all seven breeding pairs

Since its inception in 2005, clinical thiamine deficiency had never been seen in adult foxes at the breeding station. Thus, the coinciding onset of severe clinical symptoms in two males, and links to the altered (previously fresh, now frozen and approximately 18 months old) food supply, were striking. Since thiamine deficiency arises in response to low thiamine levels and/or high levels of thiaminase activity in the food, and all foxes received the same food, it is therefore conceivable that other foxes would have been subjected to subclinical levels of thiamine deficiency. Susceptibility to thiamine deficiency differs between individual animals (Witt & Goldman-Rakic 1983), and this may therefore explain why only two of 14 foxes developed advanced clinical symptoms. Given that the foxes are housed in large outdoor enclosures and are generally shy, close-up observations of the animals are rare. This, in combination with extremely subtle or non-existent symptoms related to less advanced thiamine deficiency, makes the detection of such very difficult. During the same period however, two individuals were observed vomiting, which may too be indicative of thiamine deficiency (Chang et al. 2017).

Mating in Arctic foxes occurs during March–April each year and although variable, most pups are born between mid-May and mid-June. The thiamine-deficient males thus displayed clinical symptoms during the annual reproductive period. During the preceding 17 years, a complete failure in reproduction, from all breeding pairs (typically eight breeding pairs), had never been recorded. During 2021, for example, all six breeding pairs produced pups, although one litter, born to a female beyond peak reproductive age, was lost soon after birth. In 2022, seven breeding pairs were accommodated at the station, yet not a single litter was produced. Although rarely observed, mating behaviour could be confirmed as retrospective analysis of surveillance camera footage and camera trap images fortuitously recorded mating in three of the seven pairs. Arctic fox females can reproduce from their first year and all seven females were between 1 and 5 years of age in 2022 and should therefore have been expected to produce offspring. None of the females were observed to be pregnant (visibly apparent during the final 7–10 days of pregnancy).

Based on the above, we postulated that all foxes (male and females) were exposed to subclinical levels of thiamine deficiency. The importance of thiamine for reproduction has been well documented in diverse animal groups, including fish (Ghiasi et al. 2017), birds (Mörner et al. 2017) and mammals (Nelson & Evans 1955). During pregnancy and periods of rapid growth (young individuals), increased levels of thiamine are required, further increasing potential complications associated with subclinical thiamine deficiency.

Conception and successful pregnancy are dependent on thiamine. Laboratory studies have showed that rats deprived of thiamine 11–22 days before breeding (yet lacking any clinical symptoms) resulted in 89–100% resorptions or failed implantation (Nelson & Evans 1955). However, females fed on the same thiamine-deficient diet but injected daily with progesterone and estrone resulted in 96% of females maintaining pregnancy (Nelson & Evans 1955). Thiamine deficiency can inhibit the production and circulation of key pregnancy hormones such as progesterone and oestrogens, without which reproduction is not possible. In female foxes, oestrus is associated with increased luteinising hormone, oestradiol and progesterone concentrations (Møller et al. 1984), the timing of which coincided with the development of clinical symptoms in the two breeding males.

Detrimental effects of thiamine deficiency on reproduction are not necessarily restricted to females, as spermatogenesis is inhibited in males as a result of impaired testosterone production, and thiamine is essential for testosterone production (Fleming et al. 2003; Hassan et al. 2020; Oishi et al. 2004). This may be particularly relevant to Arctic foxes which do not maintain sperm production year round (Nieminen et al. 2004). Males undergo rapid testicular growth and spermatogenesis during the early spring, and this depends on the increase of circulating luteinising hormone, follicle stimulating hormones and androgens (Smith et al. 1984; Smith et al. 1985). Thus, although only two males presented with symptoms, it is consequently plausible that the failed reproduction could have resulted from one or both sexes being adversely affected by thiamine deficiency. It was not possible to determine whether the pairs potentially failed to conceive, whether embryos were resorbed, or whether young were aborted.

On 20 and 21 July 2022, 11 of 14 foxes (five males, six females) were trapped and blood samples taken. Sampling was not undertaken earlier in case females were pregnant or had pups (not easy to determine/observe in the large enclosures). Haematological and serum chemistry analyses are presented in Table S1. Since there is a dearth of information on reference values for these blood parameters in Arctic foxes, we have supplied all information such that it is accessible to others, although not necessarily related to thiamine deficiency.

2 | TESTING OF FOOD

Shortly after the foxes were diagnosed with thiamine deficiency, food samples were taken and sent for analysis (Eurofins Food & Feed Testing Norway AS). At this point, both males still had clinical symptoms and, following their successful treatment, the one individual redeveloped symptoms later on. While the testing only provided a snapshot in time, the tests revealed that thiamine hydrochloride values ranged between 14.9 and 15.6 mg/kg, providing more than enough thiamine for the foxes' dietary requirements. While thiamine hydrochloride is hygroscopic and the accumulation of moisture during the thawing of food prior to feeding may have lowered thiamine levels, it is unlikely that this alone would have resulted in thiamine deficiency. The fish-derived thiaminase in the diet, and its activity within the foxes' digestive tracts, is therefore the most plausible cause of the thiamine deficiency. A new and alternative feed supplier was sourced and phased in from the start of October 2022. One year later, all foxes were in good health with no indications of thiamine deficiency, and four litters were produced.

To rule out the potential presence of harmful food-borne bacteria, which may have resulted in undetected loss of pregnancy, DNA metabarcoding of food samples was conducted (see Supplementary Methods). The most common bacterial causal agent of spontaneous abortions in canids (*Brucella canis*) (Pretzer 2008) was not found among the 78 bacterial taxa recovered (Table S2). *Campylobacter* species, endotoxin producing *Escherichia coli* strains, beta haemolytic *Streptococcus* and *Listeria monocytogenes* have also infrequently been linked to pregnancy loss in canids (Pretzer 2008), but none of these taxa occurred in the food samples analysed either. A number of bacteria are known to produce thiaminolytic enzymes, including *Paenibacillus thiaminolyticus* and *Clostridium thiaminolyticum*. Although a *Clostridium* species was among the most common bacteria observed in one of the food samples, it could not be definitively linked to a thiaminolytic species and is considered unlikely to have contributed to thiamine deficiency in the foxes.

3 | CONCLUSION

When the two males were diagnosed with thiamine deficiency, it was initially suspected that food thiamine levels may have been inadequate, perhaps as a result and combination of freezing, long-term storage, thawing and the effects of fish-derived thiaminase. This suspicion was pertinent given that this was the first time that the foxes had received food which had been stored for a prolonged period (18 months). Although the testing of food samples post-thiamine deficiency diagnosis are not necessarily representative of the values in the food batches utilised a few months earlier, all evidence suggests that thiamine levels in freshly thawed food were adequate. Given the confirmed incidence of thiamine deficiency, this rather points towards a strong physiological effect of thiaminase in the foxes. The combination of relatively high thiamine levels in the food may in fact explain why the clinical symptoms did not progress and lead to death, as reported in many other species, including farmed foxes (when fed on fish-dominated diets in the absence of thiamine supplementation; see for example Jones (1943)).

A detailed understanding of biochemical reactions associated with thiaminase enzymatic activity are still a topic of study (Edwards et al. 2023). Thiaminase cleaves thiamine molecules rendering them biologically inactive, and require a co-substrate to facilitate this process (usually an amine or sulfahydryl-containing compound). Once the thiamine molecule is cleaved the body is unable to restore it. Consequently, when significant amounts of thiaminase are ingested, thiamine deficiency may develop even when the concentration of dietary thiamine are adequate. We believe that this is the most likely explanation for the development of thiamine deficiency in the Arctic foxes, as tests revealed substantial levels of thiamine in the feed. Thus, although our case study consisted of a limited sample size, we believe these findings are relevant to not only captive breeding facilities, but for facilities housing carnivores in general.

Furthermore, recent work has shown how the presence of other compounds, including other B-vitamins, may either promote or inhibit thiaminase activity (Edwards et al. 2023). Consequently, dietary cofactors may potentially influence the rate and bioactivity of thiaminase present in a food and subsequent activity in the digestive tract. We do not understand what underlying factors altered the food quality, but this is suspected to have arisen due to the long-term storage, which could potentially have compromised the integrity of other (non-thiamine related) food components. This may consequently have resulted in the release or synthesis of compounds that promoted thiaminase activity, thereby resulting in clinical and subclinical thiamine deficiency in the Arctic foxes.

Of the 14 foxes, only two males displayed clinical symptoms associated with advanced stage thiamine deficiency. Despite this, results from the blood thiamine levels did not reflect particularly low levels. Furthermore, values for the one male were lower 4 weeks later, despite a positive response to thiamine injections and almost completely resolved symptoms. This again highlights the frequent difficulty in diagnosing thiamine deficiency based on blood work, even when advanced clinical symptoms are present. Furthermore, this case report based on a limited sample size highlights the challenges associated with detecting and diagnosing subclinical levels of deficiency, even though this may have pronounced effects on physiology, including reproductive capabilities (Fleming et al. 2003; Roecklein et al. 1985). A multifaceted approach, potentially combining conventional blood work with quantification of thiaminase activity in food and faeces, may prove insightful.

AUTHOR CONTRIBUTIONS

Conceptualisation; data curation; investigation; project administration; writing – original draft: Craig Jackson. *Investigation; project administration; writing – review and editing*: Marianne Furnes. *Writing – review and editing*: Lars Rød-Eriksen. *Investigation, writing – review and editing*: Kang Nian Yap. *Investigation; methodology; writing – original draft*: Marie Davey. *Investigation, writing – review and editing*: Frode Fossøy. *Writing – review and editing*: Øystein Flagstad. *Writing – review and editing*: Nina E. Eide. *Investigation; methodology; project administration; resources*: Toralf Mjøen. *Conceptualisation; data curation; investigation; methodology; project administration; writing – original draft; writing – review and editing*: Kristine Ulvund.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the article and the accompanying supplementary material.

ETHICS STATEMENT

This case study was not a planned research project, hence there was no experimental design that required ethical approval. The Arctic fox captive breeding station is approved by the Norwegian Food Safety Authority as a research facility (Facility number: 150).

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